The New England
Journal of Medicine

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Volume 230 May 18, 1944 Number 20

THE HISTORY OF THE DISCOVERY AND ISOLATION OF THE FEMALE SEX HORMONES

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I SWEAR by Apollo, the physician, and Aesculapius, and Hygeia, and Panacea, and all the Gods and Goddesses . . . [that] I will not give a woman a pessary to cause abortion." Thus reads the Hippocratic Oath, to which every physician swears, and thus for the first time in medical ethics the Greeks recognized the sanctity of motherhood. Yet even in the Greek civilization of Hippocrates abortion was not illegal or criminal, but was merely left to the midwives, who also officiated at births and brought together suitable matrimonial candidates.

The phenomena of menstruation and pregnancy have been known to man as long as has the human race itself, but their true nature and mechanisms were not understood until fairly recent times. The word "menses" is indirectly derived from the Greek noun meaning "moon." The ancient Greeks used it to describe the monthly flow from the vagina. They regarded the menses as effect of the moon on the female organism and as a periodic cleansing of the uterus.

According to the *Áyurvéda* by Susruta,[1] of India (*ca.* 1400 B.C.), the ancient Hindus regarded the menstrual flow as an "impurity" of the seven body elements. Impregnation was considered to be easiest during the menstrual flow, and the fetus was believed to be formed by the union of the male semen with the "fiery" menstrual blood. The sex of the fetus was presumably determined by the preponderance of either the semen, which produced a male fetus, or the menstrual blood, which produced a female one. If both elements were equivalent, a hermaphrodite was created. The Egyptians of the era of Ptolemy (*ca.* 300 B.C.) already knew means by which to induce conception and increase fertility, and could diagnose pregnancy at a comparatively early stage.[1]

The true physiology of the ovaries, however, remained unknown until the seventeenth century. Theodore Kerckring[2] (1643–1693), of Amsterdam, was one of the earliest to state that the "ovum" — as the ovarian follicle was then called — was expelled by the onset of menstruation or by sexual excitement. This view was disproved in 1843 by Ritchie,[3] who demonstrated that menstruation and ovulation were dependent on each other and that ovulation determined menstruation. Yet it was not until 1927 that Corner[4] proved that even menstruation may occur without ovulation. Hejdentrijk Overkamp[5] (1651–1692), a contemporary of Kerckring, believed that the "ova" — that is, follicles — formed a substance that passed into the general circulation. The Frenchman Nicholas Venette[6] (1633–1698) called this substance "the spermatic vapors" and believed that it produced menstruation after entering the systemic circulation. François Mauriceau[7] (1637–1709) was the first to suggest that conception was not dependent on menstruation, and Bischoff[8] in 1844 proved that the ova matured periodically and independently of coitus. The concept that the primary function of the uterus is pregnancy and that menstruation is merely an indication of the thwarting of this function is therefore of modern origin.

It is of historical interest to observe that some of the earliest indications of the variability of the abnormal female sex characteristics that today are recognized as embryologic or endocrine disorders were expressed in the artistic creations of ancient and medieval origin. At least two types of mixed-sex personalities can be detected in the classic sculptures and paintings: virilism and hermaphroditism. Antique statuary unearthed by excavations in Asia Minor, Greece and Italy show these two distinct types; for in those times it was the acme of sculptural endeavor to adorn men with feminine characteristics, and women with those of men. Perhaps the best-known example of virilism in women is the famous statue of Psyche, the mistress of Eros, now preserved in the Museum of Naples. This figure exhibits small and flat breasts on a wide masculine chest and a long body of straight lines terminating in a small pelvis. Hippocrates describes in his

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Epidemics two women with marked facial hirsutism during the menopause.[9] Many artistic works and even modern side shows still attest to the prevalence of this curiosity. Archaeological research indicates that the inhabitants of the island of Cyprus in the eastern Mediterranean in antiquity worshiped a bearded female deity, part of a cult imported from the East, but no sculptures portraying this goddess have been unearthed.[10]

The hermaphroditic statues of the ancient Greeks were frequently sculptured after living models, but some were based on an ideal concept that incorporated the most aesthetic features of both the male and the female bodies. The best examples of this natural hermaphrodite statuary are preserved in the Villa Albani in Rome, where the art-loving Cardinal Albani (1692–1779) assembled an exquisite collection during the eighteenth century; in the State Museum of Berlin; and among the art objects in the Museum of Naples, from those that were excavated at Herculaneum, the city destroyed together with Pompeii by the eruption of Vesuvius in 77 A.D. These hermaphrodites possess a predominantly female body contour adorned with male genitalia.

The best sculptures of natural hermaphrodites were unearthed in the Necropolis at Myrina in Asia Minor. These statuettes, which are of terra cotta, display composite characteristics of both young men and young women. They show a delicately rounded neck and generous fatty pads, especially on the buttocks, hips, thighs and pubes. The abdomen is slightly protruding, but the face shows a delicate and gracious feminine expression. The well-formed breasts appear small, and the extremely small external genitalia are those of the male.

The masters of the Renaissance likewise preferred females suggestive of hypogonadism. The portraits by Botticelli (1447–1515) depict women with small breasts, a long neck and long extremities, as in the paintings "Truth and Repentance" and "The Birth of Venus," now in the Art Galleries in Florence. A similar trend is seen in the Flemish brother-painters Van Eyck, who lived in the fifteenth century. Jan Van Eyck's "Eve" and "The Love Spell," by one of the pupils of the Van Eycks, now in the galleries of Leipzig, are examples of this trend. The Museo de Prado in Madrid has a painting of the crucifixion of the "bearded" Saint Wildegeforth. The Spanish master Ribera (1588–1652) portrayed himself together with Madelaine Ventura, also a bearded woman, who is shown nursing an infant.[11]

Perhaps the earliest medical conception — or rather misconception — of the value of glandular products found its expression in organotherapy — that is, in the medicinal use of various animal and human tissues and excretions for the express purpose of deriving certain specific physiologic effects from their use. In fact, materia medica, and especially therapeutics and endocrinology, have sprung from this type of remedial custom of primitive races and ancient civilizations. The primitive tribes had already observed how some animals — and among these even the herbiverous cow — swallowed the placenta after their young had been born. It was therefore logical to assume that placental tissue would arrest post-partum hemorrhages, stimulate milk secretion and even cure sterility. The long survival of primitive organotherapy was due primarily to popular superstition and a belief in magic powers, and had no scientific basis. One reads today with amazement of such customs as eating one's enemies or the organs of certain animals to acquire their particular qualities.

The rationale of medieval substitution therapy was well formulated by Thomas Vicary[12] (1490–1561) when he wrote in 1548 that "in what part of the body the faculty which you would strengthen lies, take the same part of the body of another creature in whom the faculty is strong, as a medicine." Organotherapy has prevailed until recent times, and even today is practiced to certain degrees, although it has become limited to the "glandular pills" and "desiccated polyglandular" nostrums heralded by modern superadvertising campaigns of exploiting patent-medicine makers. Landouzy[13] in 1898, at a time when the so-called "invigorating" effects of glandular concoctions were blatantly publicized, and when the real functions and actions of the glands of internal secretion were beginning to be scientifically investigated, suggested "opotherapy" as a substitute for the old word "organotherapy" — perhaps to avoid the evil connotation of the latter word, or perhaps because he realized the secretory function and nature of these glands. The name "opotherapy" Landouzy derived from the Greek nouns οπος, "juice," and θεραπεια, "treatment," but this word never found scientific or popular favor.

Dana[14] in 1916 conferred the title "Author of Opotherapy and Endocrinology" on Joannes Ursinus,[15] a French physician-poet, who wrote *Prosopopoeia animalium aliquot* in 1541. This is an elegiac poem in which Ursinus describes the remedial value and uses of seventy-five animal preparations. Ursinus thus by more than a century preceded Johann Joachim Becher[16] (1635–1682), whose *Parnassus medicinalis illustratus*, written in 1663, dealt with the animal, vegetable and mineral remedies of his time. This remarkable book, written much in the style of the Health Rules of Salerno, both in verse and in prose, contained in four parts more than one thousand pages and twelve hundred illustrations. It mentioned forty animal and twenty-five human substances that supposedly had some remedial value.

Limiting organotherapy to the specific employment of the excretory sex products of the female, either animal or human, which, as is known today, contain certain hormonal ingredients, one finds a

protean assortment of these in ancient and medieval — and even modern — therapeutics. A few of the more repulsive substances and the blatant claims for these remedies will be mentioned.

According to the *Papyrus Ebers*, which is generally dated at about 1550 B.C., the ancient Egyptian pharmacopoeia contained over one hundred groups of preparations, and at least forty of these were animal or human excretions.[17] For instance, the urine of a spouse who had remained faithful to her husband and had known no other man was a remedy for sore eyes. Herodotus[18] (*ca.* 500–424 B.C.) tells the story of the Egyptian king Pheron, the son of Sesostris, conqueror of Egypt, who had to search diligently for ten years before he could obtain this medicine. He had tried the urine of his wife and of many other women without results. At last he succeeded, married this woman and burned all the others to death — quite a commentary on the morals of those times. Among the ancient Hindus, propagation began with religious ceremonies. Immediately preceding intercourse, an ointment prepared from the dried and powdered penis of a bear and the perirenal fat of a tiger (the kidneys were then regarded as the semen-producing organs) was applied for "prompt action." Bourke[19] relates many similar tales.

Among the ancient Romans the *Natural History* of Cajus Pliny the Elder[20] (23–79 A.D.), who inveterately disliked all physicians, tabulated more than two hundred and fifty remedies of animal or human origin, as compiled by four hundred and seventy-three earlier authors. Pliny[20] spoke highly of the medicinal virtues of menstrual blood, not only for the cure of certain diseases but also for killing insect pests at a distance and for quelling storms at sea. Yet it would spoil wine, and dogs licking it would become mad.

In the Middle Ages the Dominican monk Albertus von Bollstädt[21] (1193–1280), later Bishop of Regensburg, better known as Albertus Magnus, taught at the universities of Paris and Cologne. While lecturing at Paris he recommended powdered testes of hogs in wine for men with poor sexual powers, and powdered uteri of hares, similarly prepared, to render sterile women fertile.[21] Rondelet,[22] of Montpellier (1507–1566), is credited by Rolleston[23] with a prescription advocating the dried powder of placenta for the uncomplicated expulsion of the retained secundines after delivery.

Even today such substitution therapy still prevails in the less civilized countries of Europe. The Serbs, for instance, believe that nothing is better for the treatment of impotence than a few dashes of the urine of a pregnant mare, taken in a glass of water.

In this connection should also be mentioned the rejuvenation fad of three decades ago. Rejuvenation in women is even more problematic and uncertain than that in men. The observation of Steinach and Holzknecht[24] that roentgen rays applied to the female pelvis act similarly to vasoligation in males, and that although harming the generative functions of the ovary they produce a proliferation of the ovarian interstitial cells, has not been found true. Zondek[25] criticized this theory by stating that Steinach disregarded the fact that during the menopause the follicles are destroyed and that only certain connective tissues remain, holding that not enough interstitial cells that can be stimulated are left. He also attacked as unfounded the suggestion of Liepmann[26] that hysterectomy can produce rejuvenation by reason of ligation of the ovarian tubes, and concludes: "On the whole, therefore, the attempts at rejuvenation are hardly adapted to induce an actual renascence of aged human beings. Such endeavors cannot, indeed, be assumed to harmonize with nature's plan of organization."

Although the existence, not necessarily the function, of the testes was known to ancient civilizations because of their external location and easy accessibility, that of the ovary was often not even suspected. Herophilus of Alexandria (*ca.* 300 B.C.) is credited by Galen[27] with the anatomical discovery of the uterine tubes — or *meati spermatici*, as he called them — and with the "female testes," or *testes muliebris*. He also believed that the male and female semens were transmitted through the "spermatic vessels" and that the tubes passed from the "female testes" to the neck of the bladder, a conception later disproved by Galen.

The Greeks of the Hippocratic era did not know of the existence of the ovaries and thought that the "female semen" was produced as the vaginal secretion during coitus.[1] They believed that conception occurred most easily during the menstrual flow, when girls were conceived, whereas the period immediately after the flow was optimal for the procreation of boys. In this respect their views coincided closely with those of the ancient Hindus. Athenaios of Attalia in Cilicia (*ca.* 70 A.D.) considered the "female testes" as well as the male breasts as simple symmetrical appendages.[1]

Castration of women was already practiced by the ancient Hindus, and Tillmanns relates that even the aboriginal Australian tribes performed operations for artificial hypospadias and ovariectomy to produce impotence and sterility among the unmarried members of their tribes, thus facilitating unproductive sexual intercourse among them.[1]

For nearly fifteen hundred years after Herophilus there was little advance in the anatomical knowledge of the female gonads. The discovery of Herophilus was probably lost in the destruction and fire of the great Library of Alexandria by the Arabs in 640 A.D. Galen reigned supreme, although his anatomical concepts were based to a large extent on fancy. So great was the authority of Galen that

Henri de Mondeville (1260–1320) exclaimed with reckless courage "God did not surely exhaust all His wisdom in the creation of Galen."[28]

The *De Fabrica*, by Vesalius[29] (1514–1564), gives an account of the irregular surface of the "female testes," as the ovaries were still called. The name "ovary" originated in 1621 when Fabricius ab Aquapendente[30] (1537–1619), who believed that the ovaries contained the "female semen," introduced this name after observing the ovaries of hens. "Ovary" was first applied to human beings in 1667 by Niels Stensen[31] (1648–1686), who suggested that the vesicles or "blisters" in the female testes were the ova. Also known as Nicholaus Steno, a brilliant student of anatomy, his fame is still associated with the eponym of the excretory duct of the parotid gland and of several other anatomic structures. He is one of the most famous truants of medicine, having at the height of his fruitful scientific career deserted anatomy to find salvation in the Catholic faith and to become titular Bishop of Titiopolis. He returned to Copenhagen and remained there for a while as professor of anatomy, and propagated his new faith, but mental conflicts soon forced him to resign again. He died a short time later at the early age of thirty-eight.

Gabriele Fallopio[32] (1523–1562), another famous anatomist, successor to Vesalius at the University of Padua, published his *Observationes anatomicae* in 1561. In this book he described in detail the ovaries as well as the uterine tubes, now known by his name, although he did not discover them. He had also observed the corpus luteum, which he described as "velvety vesicles filled with water or a watery fluid sometimes yellow, sometimes like a truly clear swelling." Both Fallopius and Stensen believed that the ovarian follicles were true ova. It was left to the former's pupil Volcherius Coiter[33] (1534–1590) to publicize this observation in 1573, crediting his teacher with it. Coiter himself believed that the ovaries corresponded to the seminal vesicles rather than to the testes and stored the female semen.

The "yellow body" of the ovaries, however, was not described fully or known by this name until Marcello Malpighi[34] (1628–1694) studied it carefully with a crude microscope and called it the "corpus luteum" in the appendix (*De ovo incubato*) to the first volume of his *Opera* published in London in 1686. He had found it in virgin as well as in pregnant animals and believed it to be the substance that gave rise to the ovarian follicles, then known as the "ova." De Buffon[35] (1708–1788), a Frenchman, however, regarded it as a transient gland that secreted the seminal fluid of the female. It was not until 1766 that Albrecht von Haller[36] demonstrated that the corpus luteum was formed by a thickening of the wall of the graafian follicle after its rupture. From this time on the corpus luteum and the follicles were studied in their true physiologic relation.

In 1668 there appeared a book entitled *The Male Generative Organs*, by Regnier de Graaf[37] (1641–1673), of Schoonhaven, Holland. In this book is the first account of the nature of the ovarian follicles, then called "ovula." There followed four years later a more detailed study in *De mulierum organis generatione inservientibus*.[38] The reasons for the original preliminary note and the subsequent detailed elucidation of the same subject can be found in one of those disputes over priority in which several investigators simultaneously made the identical discovery. There exists a letter of 1668 — unpublished until 1672 — to Werner Rolfink (1599–1673) by J. C. van Horne[39] in which he described the discovery of the ovarian follicles, then known as ova, prior to de Graaf's first announcement. For details of this chapter in the history of anatomy the reader is referred to the essay of Corner.[40] De Graaf did not claim priority for his observation. In fact, he spoke of the celebrated van Horne's having made this discovery, but von Haller[36] in 1766 coined the eponym "Graafian" vesicle or follicle, because of the detailed study by de Graaf, who rightfully deserves this credit. De Graaf also gave a detailed account of the corpus luteum, describing it as a glandular substance that formed herniations on the "female testes," and foresaw that the ovary formed ova. Rosenmüller[41] in 1802 described originally the epoöphoron, later known eponymically as the "organ of Rosenmüller" or parovarium. The actual human ovum was finally discovered in 1827 by von Baer[42] after many failures by other investigators.

The general historical background, as well as the development of the nomenclature peculiar to endocrinology, has recently been compiled with special reference to the male hormone.[43] A few pertinent notes, however, may be added. The famous physiologist Hufeland[44] (1762–1836), while a professor at the University of Göttingen, made this interesting statement in 1797: "The organs of generation have the power of secreting the finest and most spiritual parts of our nourishment. But at the same time they are so organized that these perfected and ennobled juices can again return and be received into the blood." Whether this was merely an adaptation of de Bordeu's theory or an original thought is difficult to ascertain. In a fundamental paper King,[45] of Guy's Hospital, London, in 1836 described the structure and function of the thyroid colloid, and demonstrated its passage into the lymphatics and blood stream as "indirectly surmised by Morgagni." His concept of true endocrine function seems well substantiated in the following excerpt:

> Yet we may one day be able to show that a particular material is slowly formed and partially kept in reserve, and that this principle is also supplementary, when poured into the descending cava, to important functions in the course of its circulation, [and] the influence which it exerts upon the circulating fluid may be more or less needful for the healthy subsidence of the entire animal.

In English medical literature the term "endocrinic" was first used casually by Crookshank[46] in February, 1914. In the United States, Halsted,[47] in one of the Harvey Lectures of the same year, referred to the endocrine glands as "hormonopoietic." Blair Bell[48] in 1917 criticized the noun and the adjective "endocrine" and proposed in their stead the words "hormopoiesis" and "hormopoietic," respectively, for the ductless glands, a suggestion probably derived from Halsted's lecture. Abderhalden[49] in 1924 had suggested the word "incretions" for the internal secretions to differentiate them from the "excretions" (waste products), a name originally proposed by Roux in 1919. None of these terms, however, found popular favor, and all soon lapsed into oblivion.

In contradistinction to the singular testicular hormone so far known, the female sex hormones consist of at least two distinct principles: the luteal and the follicular factors, referred to as the progestins and the estrogens. It may be stated that the concept of hormones peculiar to a specific sex, or specific in their action, is no longer valid. Both types of sex hormones occur in either sex in a quantitative relation, and their action depends on the quantitative level and physiologic pathology rather than on specificity. It is preferable, therefore, to speak merely of sex hormones with androgenic or with gynecogenic actions.

At a time when the anatomy of the ovaries and the action or function of their products became known, the general study of endocrine secretions reached the stage of experimental investigation. Yet it is interesting to observe that the hormonal activities of the female gonads were among the last to be suspected, and their principles among the last to be isolated.

Sir Percival Pott[50] (1713–1788) gave one of the earliest descriptions of the effects of castration of mature women, and the gynecologist Battey[51] (1828–1895), of Rome, Georgia, was among the first to suspect an endocrine function — or rather dysfunction — of the ovaries. In August, 1872, the latter performed the first ovariectomy for physiologic reasons, an event that again led to an acrimonious dispute with English surgeons who claimed priority. Battey had excised the normal and healthy ovaries for the relief of functional disorders, an operation done first only one month earlier at Freiburg, by Hegar. The latter's patient failed to survive, so that Battey deserves the credit for arriving independently at this decision. The rationale of this operation has since been amply justified by the discovery of certain specialized cells in the ovary that have an endocrine function, and the imbalance of which may lead to functional disorders.

Regis[52] in 1893 claimed that the psychoses of the surgical menopause could be cured by the injection of ovarian juices. His ideas may have been stimulated by the claims of Brown-Séquard[53] with testicular extracts. Curàtullo and Tarulli[54] in 1896 suggested an endocrine function of the entire ovary. Knauer[54] in the same year observed atrophy of the uterus after removal of the ovaries, but was able to prevent this involution by transplanting ovarian tissues into the castrated animals. Halban[55] in 1900 demonstrated that ovarian skin grafts brought about normal puberty in guinea pigs castrated in infancy. Adler[56] in 1912 achieved similar results with crude watery extracts of the ovary when desiccated tissues had failed.

It was at the turn of the last century that Prenant[57] and Born[58] independently suggested that the corpus luteum had an endocrine function essential for the maintenance of pregnancy. Clark[59] in 1900 differentiated between the "true" corpus luteum of pregnancy and the "false" one of menstruation, and Corner[4] in 1927 finally proved that the corpus luteum is not essential for the occurrence of menstruation. Fraenkel,[58] a pupil of Born, believed the yellow body to be the only source of hormone production in the ovary. Loeb[60] in 1907 demonstrated specifically that the corpus luteum hormone prepared the uterus for nidation of the fertilized ovum by producing certain progestational changes in the endometrium, irrespective of whether pregnancy follows. If pregnancy did not take place, its effects resulted in a desquamation of the uterine mucosa — that is, in menstruation. Finally, Fraenkel[61] in 1910 proved the endocrine function of the corpus luteum.

Long before anything was known about the corpus-luteum hormone, physicians differentiated "desiccated whole ovary" and "desiccated corpus luteum" preparations. It was then not realized, however, that neither had any therapeutic effects, since the concentration of hormones in them was negligible. It is claimed that virtually tons of desiccated ovarian tissue would be necessary to produce even minor estrogenic effects, and that no effective amounts of corpus-luteum hormone could ever be administered by such "ovarian pills." Frank[62] stated in 1931 that "such things as desiccated ovary, desiccated testes, thymus and anterior-pituitary extracts can be given by pound or bushel, and the only effect that I can notice is a disturbance of a delicate stomach."

The qualitative as well as the quantitative determination of the luteal hormone — or of any hormone — depends entirely on reliable methods of detection and assay. The ideal methods are those of chemical reactions, but these, as in so many other endocrine products, are not yet feasible. Recourse has therefore to be taken to biologic methods. For this purpose there are available two methods for the assay of the luteal principle. The first, discovered by Corner and Allen[63] in 1929, utilizes a sexually mature rabbit, since its ovaries always contain ripe follicles, and since its uterine mucosa is always in the proliferative stage. An injection of

luteal extracts or of pure hormone transforms this mucosa into a "prepregnant" or "pseudopregnant" state.

The second method was developed by Clauberg[64] in 1930, and consists of bringing the infantile uterine mucosa of an immature rabbit into the proliferative stage by preliminary injections of follicular hormone. This is usually achieved after eight daily injections of ten mouse units. The luteal hormone to be assayed is then injected until a pseudopregnant uterine mucosa develops. The smallest amount of luteal hormone that will produce this result is the unit of potency, or rabbit unit. The standard, or international, unit was determined at the International Conference for Biological Standardization in London in 1935.[65] It is the equivalent of 1 mg. of the crystalline corpus-luteum hormone (beta progesterone) preserved in London.

Practicing physicians waited anxiously for a pure corpus-luteum extract, since many uses and indications had been theoretically foreseen. Hannes[66] in 1919 attempted to prevent spontaneous abortion with crude extracts. The mechanism of premenstrual tension was postulated by Frank[62] in 1931, and Novak and Reynolds[67] in 1932 defined the motility factors underlying functional dysmenorrhea. Engle and his co-workers[68] after a series of careful studies suggested the importance of the luteal principle in the functional uterine bleeding disorders.

Weichert[69] in 1928 demonstrated the action of the corpus luteum hormone by the observation of definite changes in the uterus of animals, as previously described by Loeb[60] in 1907. For his experiments he used crude corpus-luteum extracts and injected them into the test animals. His claims were soon confirmed by other investigators. Corner and Allen[63] in 1929 prepared the first crude extract of luteal hormone from the ovaries of swine. Allen and Wintersteiner[70] and Butenandt and his co-workers[71] in 1934 succeeded in isolating a crystalline form of the hormone. They determined its structure as a di-keto-steroid, with the empirical formula $C_{21}H_{30}O_2$. The final achievement, however, was the synthetic production of this hormone in pure form by Butenandt's[72] laboratory, and soon by others, who prepared it from the stigmasterol portion of soy beans. This synthesis made possible extensive clinical study and application, since the hormone was completely reliable and free from other related compounds and side effects.

It is interesting to note that the natural hormone occurs in an extremely small relative quantity, in a ratio variously estimated as 1: 40,000 in the human corpus luteum and 1:750,000 in the human placenta. The pure principle is now also synthetized from pregnanediol,[73] a progestin and excretion product found in pregnancy urine. The clinical results obtained with the pure hormone have substantiated the theoretical predictions, but even today its effects have not been explored in their entirety. Clinical results depend on a chemically pure hormone of exactly known potency and of complete reliability.

The early terminology of the corpus-luteum hormone was variegated and confusing, because of the numerous nonproprietary and proprietary names for the same substance. Corner and Allen[63] called it "progestin" on account of its progestational activity. Hisaw preferred the name "relaxin"[74] for one principle because of its ability to relax the sacral and pubic ligaments in pregnant rodents, and the name "corporin"[75] for a similar factor because of its origin in the corpus luteum. Clauberg[64] used the names "lutein" and "proluton" for similar reasons, and Slotta[76] coined the terms "luteo-steron C and D" because of the steroid nature of the compounds. Finally, to prevent further confusion the leading investigators from all countries met in 1935 and agreed to use henceforth only the term "progesterone,"[77] which proved acceptable to all and is now the nonproprietary designation for the luteal principle. It is, however, limited to the pure crystalline hormone, the term "progestin" being used to denote the whole group of progesterone-like, or impure, substances.

Chemically, progesterone, as isolated in 1934, is pregnenedion-3-1-20-ol, and has the empirical formula $C_{21}H_{30}O_2$. It exists in two isomeric forms in the solid state only, and either of these forms can be easily converted into the other. In solution both forms are chemically and physiologically identical. Progesterone is synthetized from the stigmasterol portion of soy beans and from the pregnanediol of pregnancy urine. The orally effective derivative pregneninolone was discovered by Inhoffen and Hohlweg[78] in 1938 by the addition of an ethinyl radical to the follicular or the androgenic principles.

Although the corpus-luteum principle was at first the only female hormone suspected and sought, the early investigators soon realized that there must be at least another factor — and source of hormones — in the ovary. Marshall[79] in 1905 suggested that either the interstitial or the follicular cells of the ovary also secreted a hormone that would produce estrus. Halban[80] in the same year found that this follicular factor stimulated growth of and produced changes in the breasts. Adler[56] in 1912 produced estrous changes by the injection of watery extracts of the ovaries into virgin animals. Iscovesco,[81] and independently Fellner,[82] and several others in the same year prepared certain lipoid extracts of the ovary that produced hyperemia in the uterus of castrate and immature rodents.

The name "estrus" is the same as the Latin word for gadfly, and was used figuratively to indicate intense sexual frenzy or heat in animals. It designates the restricted period of mating activity of female mammals, but not that of the primates. Recent experiments with the ovarian hormones have em-

phasized another aspect of estrus — namely, the rapid growth of the accessory sex organs. This growth introduces the period of rut proper, and is brought about by the follicular hormone. The follicular hormone is therefore primarily a growth hormone, whereas the luteal hormone does not have this property.

The earliest test for the follicular factor was developed by Aschner[83] in 1913. He had observed in castrated female rodents growth of breasts and nipples and hyperemia of the vagina and the uterus three to seven days after the injection of ovarian and placental extracts. When Stockard and Papanicolaou[84] in 1917 discovered a typical estrus cycle in the guinea pig the phases of which could be accurately determined by the presence of certain cornified epithelial cell changes in the vaginal smears with beginning rut, an important forward step was made. This phenomenon was utilized by Allen and Doisy[85] in 1923 to develop a method for studying qualitatively the actions of this hormone. They observed changes from the normal leukocytes of the vagina of castrated rodents to cornified epithelial cells and squamous scales two or three days after the injection of follicular extracts, changes that occurred normally only in estrous females. Simultaneously they announced for the first time the isolation of a comparatively pure crystalline substance obtained from the follicular fluid of cows and sows, 3 mg. of which induced estrus in a rat; this amount they called "1 rat unit."

Less popular tests were developed in 1925 by Frank,[86] who claimed that the delay in contractions of the uterine strip when suspended in Ringer's solution was in proportion to the concentration of preceding hormone saturation. Blotevogel[87] noted an increase of the chrome-staining cells of the pericervical lymph nodes of castrated animals after injection of active follicular substances.

With such growth-indicators as measures of qualitative and quantitative biologic changes, the other sources of estrogens could be found and assayed in animal organs as well as in plants, and even among minerals. The collective term "estrogenic principle" refers to any substance that induces the growth of the accessory sex organs.

Courrier[88] in 1924 studied the action of this hormone on the menstrual cycle, and because of its importance in producing the follicular phase called it "folliculin," a name still commonly used. A year later Laqueur[89] coined the term "menformon," now used as a proprietary name. Glimm and Wadehn[90] preferred the word "feminin" for this principle. In 1925, Loewe[91] demonstrated the occurrence of follicular substances in the urine and the blood of normal women and called it "thelykinin" to signify its feminine activity. Collip[92] named it "emmenin" after obtaining it from the placenta. It is to the credit of Parkes and Bellerby[93] to have introduced the term "oestrin" in 1926, a name later modified to "estrone," designating the nonproprietary form for the follicular hormone.

Estrone is a fat-soluble principle derived from sterols. It was extracted in 1927 by Doisy,[94] who named it "theelin." Butenandt[95] in 1929 independently isolated and crystallized it, with the empirical formula $C_{18}H_{22}O_2$ and called it "progynon," a term also retained as a proprietary designation. Marrian[96] in 1930 isolated the excretory form of this hormone, known then as "theelol." It soon became evident that this hormone existed in numerous chemical forms with varying degrees of physiologic action.

The basic structure of the follicular principle is estratriene $C_{18}H_{21}$, empirically identical with estrane, the basis of all sex hormones, female as well as male. Estrone, or 17-keto-3-hydroxy estratriene, was synthetized by Butenandt[97] in 1933 from palm nuts, but is not the true secretion of the follicular cells. The actual hormone is estradiol, which was obtained in pure form by Schwenk and Hildebrandt[98] in 1933 by the reduction of the keto-form to an alcohol, and what has the empirical formula $C_{18}H_{24}O_2$.

To eliminate the confusion of different names and different potencies, the Health Organization of the League of Nations[99] in session at London in 1931 designated as the international unit 0.1 gamma of the pure crystalline substance estrone, since the true principle estradiol was not yet isolated. This unit is about one third as active as the original Allen–Doisy rat unit, and is based entirely on gravimetric measures. It makes no reference to the estrous effects in castrated rodents. In order to prevent misinterpretation with later preparations a second international standard was adopted in 1935 for the less potent but longer-acting benzoylated derivatives,[65] as measured by the benzoic acid ester of alpha estradiol, the di-hydro-estratriene, but even then its estrogenic equivalent to the keto-hydroxy form estrone was not defined.

The bursting human follicle contains 2 or 3 cc. of follicular fluid with an estrogenic equivalent of 8 to 12 mouse units.[25] Zondek and Aschheim[100] in 1927 demonstrated that the hormone is most likely produced by the thecal and granulosal cells of the follicle, but Allen[101] believes that all ovarian tissues may produce it, as well as the corpus luteum and the placenta. It is not peculiar to the female, for Haeussler[102] in 1934 found that the urine of stallions contains five hundred times higher titers of it than do those occurring in the ovaries of mature mares.

It is not within the scope of this essay to discuss the chemical and physiologic interrelations of the sex hormones or their clinical status, all of which command an enormous literature. Brief mention, however, should be made of the nonbiologic estrogens used clinically. There are at least forty known substances with estrogenic activity, and among these the only nonbiologic compound so far

used belongs to the stilbestrol group. Cook and Dodds[108] studied hydrocarbons intensively and found that many had estrogenic activities. Schwerdtfeger[106] in 1931 demonstrated that some sea animals and insects possess estrogenic substances, whereas Silberstein and his co-workers[105] found them in actively growing bacterial cultures. Finally, Dodds[109] in 1938 discovered the stilbene compounds, which were unusually active in minute doses, and called the basic substance 4, 4-dihydroxystilbene "stilbestrol." The most promising of its derivatives is now known by the nonproprietary name "diethylstilbestrol," or 4, 4-dihydroxy-α-β-diethylstilbene. Clinically it acts like the natural estrogens but has some unpleasant side effects. It is not a steroid and is easily and cheaply prepared from common chemical reagents.

* * *

Thus ends the story of one of the most fascinating chapters of medical history. Primitive man, limited by the faulty observations of inexperience, cannot be condemned for imitating Nature in eating indiscriminately certain excretory substances in the hope of saving his life. One must marvel at the way in which progressive minds at the risk of death as heretics tried to advance human welfare but failed because of deficient knowledge, jealously guarded by despotic authority. Yet the pendulum swung on through the depth of the dark centuries, to reach its climax in the speculative theories of a century of enlightenment. But even logic failed because it was based on erroneous premises. Finally the pendulum swung back through another century that witnessed the beginning of exact experimental science, and completed its course only a few years ago when the chemical nature of the hormones was discovered.

The speculative mind does not rest, but wonders at the ingenuity of the chemical laboratory of the human body, not yet duplicated by creative powers. Whither will it lead? The close relations of vitamins, hormones and carcinogens are known. Will the human mind finally conquer in spite of the obstacle still deemed unsurmountable? But guessing is futile — unless based on facts and proved by experiment.

So one can do no better than epitomize the past in chronological order and await the revelations of the future:

1550 B.C. The *Papyrus Ebers*, the oldest medical book known, mentions more than forty animal and human products as remedies.

1400 The *Ayurvéda* by Susruta regards menstruation as a periodic cleansing of the body, and mentions several organotherapeutic remedies for sexual disorders.

460 Hippocrates of Cos describes 2 cases of menopausal hirsutism.

Greek medical ethics recognizes the sanctity of motherhood.

The Greeks know the testes but not the ovaries.

300 Herophilus of Alexandria discovers the "female testes" or ovaries and the *meati spermatici* or ovarian tubes.

70 A.D. Pliny the Elder mentions the remedial qualities of menstrual blood among more than two hundred and fifty medicines of animal or human origin, as compiled by four hundred and seventy-three authors.

1250 Albertus Magnus recommends powdered uteri of hares as a remedy for female sterility.

1300 Henri de Mondeville assails the supremacy of Galen.

1541 Jean Ursinus, a French physician-poet, was subsequently called by Dana "the Author of Opotherapy and Endocrinology."

1548 Thomas Vicary states the rationale of organotherapy.

1555 Andreas Vesalius describes the "irregularities" of the "female testes."

1561 Gabriele Fallopio describes the ovarian tubes and the yellow body of the ovary.

1575 Guillaume Rondelet advocates dried placenta for uncomplicated expulsion of retained secundines.

1621 Fabricius ab Aquapendente describes the ovaries of hens.

1663 Johann Joachim Becher's *Parnassus medicinalis illustratus* mentions forty animal and twenty-five human substances as remedies.

1667 Niels Stensen uses the name "ovary" for "female testes."

1668 J. C. van Horne discovers the ovarian follicles, but Regnier de Graaf describes them in detail.

1691 François Mauriceau suggests that conception is independent of menstruation.

1686 Marcello Malpighi coins the name "corpus luteum."

1690 Heidentrijk Overkamp believes that the "ova" — that is, follicles — secrete a substance into the circulating blood.

1696 Nicholas Venette believe that this substance causes menstruation.

1756 Percival Pott describes the effects of removal of the healthy ovaries in a young woman.

1766 Albrecht von Haller coins the eponym "graafian follicle."

1776 G. L. D. de Buffon regards the corpus luteum as the gland that secretes the "female semen."

1802 J. C. Rosenmüller describes the epoöphoron since known by his name.

1827 C. E. von Baer discovers the human and mammalian ova.

1872 Robert Battey for the first time intentionally removes the ovaries for menstrual disorders, an operation since known by his name.

1896 Curàtello and Tarulli suggest an endocrine function of the ovary.

1898 G. Born and independently A. Prenant suggest an endocrine function of the corpus luteum.

1905 F. H. A. Marshall mentions a follicular hormone.

1910 L. Fraenkel proves the endocrine function of the corpus luteum.

1913 B. Aschner devises the first biologic test for the follicular hormone.

1919 W. Hannes for the first time uses corpus luteum extracts to prevent spontaneous abortion.

1923 E. Allen and E. A. Doisy devise the best test for, and isolate, the follicular hormone.

1929 G. W. Corner and W. M. Allen discover a biologic test for, and prepare the first crude extracts of, corpus-luteum hormone.

A. Butenandt and independently E. A. Doisy crystallize the follicular hormone estrone.

1933 A. Butenandt synthetizes the follicular hormone from palm-nut oil.

E. Schwenk and F. Hildebrandt obtain the true follicular hormone estradiol by reduction of estrone.

1934 A. Butenandt and independently W. M. Allen and O. Wintersteiner crystallize the corpus-luteum hormone progesterone.

A. Butenandt synthetizes progesterone from soy beans.

112 Vernon Street

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Vol. 19

SWEAT AS A CULTURE MEDIUM FOR FUNGI*

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CHICAGO

IT HAS been realized that sweat can support the growth of fungi and that its excessive secretion is often the determining factor in infection. It is common to observe the presence of hyperhidrosis with eczematoid ringworm of the hands and feet. One of us (T.C.[1]) has shown experimentally that such infection can be clinically induced by conditions that favor increased sweating of the feet.

The growth of fungi in sweat, as demonstrated in the experiments reported in the present paper and by clinical observations, depends on an unconcentrated medium. The same material after concentration by evaporation has antiseptic powers. Peck, Rosenfeld, Leifer and Bierman[2] have shown that thermal sweat may have fungistatic properties acid in reaction (below pH 7.0), particularly when concentrated, and that these properties depend on its content of acetic, proprionic, caproic, caprylic, lactic and ascorbic acids. They have also found topical applications of these acid ingredients of sweat to be valuable in the treatment of fungus infections.

Bergeim and Cornbleet[3] believe that freshly secreted sweat may have a mild antiseptic action,

TABLE 1. *Description of Plate Cultures.*

Type of Examination	Sweat Agar	Sabouraud's Medium
Trichophyton purpureum		
Macroscopic	The colony had the same character as when the mold was grown on Sabouraud's medium except that it was smaller and growth was not so luxuriant.	The colony produced was thick and white, with a centra umbo, and had a velvety appearance. The back of the colony displayed a typical rose-purple color. A minimum of aerial growth was present.
Microscopic	Mounts prepared from a giant colony 1 month old showed many microconidia, a few fuseaux and a racquet mycelium.	Mounts prepared from colonies showed numerous microconidia and a racquet mycelium. A fairly large number of fuseaux were seen.
Trichophyton gypseum		
Macroscopic	The colony had the same character as when the mold was grown on Sabouraud's medium, but it was smaller and growth was not so luxuriant. Two concentric zones were clearly apparent.	The colony produced was white and fluffy and had a boss at the center. It showed many aerial mycelia.
Microscopic	Mounts prepared from a giant colony 1 month old showed microconidia, a branched, segmented mycelium and a few spirals. No fuseaux were seen.	The mycelium was septate. Numerous microconidia, a racquet mycelia and several blunt end fuseaux were seen.
Microsporum gypseum		
Macroscopic	The colony grew more rapidly than those of other species but was a scant filamentous growth and attained a greater diameter than did the other colonies.	The colony showed a white, felty growth with a large central umbo. Later it assumed a yellowish color.
Microscopic	Mounts prepared from a giant colony 1 month old showed a racquet mycelium, numerous microconidia and an occasional fuseau.	Mounts showed a racquet mycelium. Numerous microconidia and fuseaux were present.
Hormodendrum species		
Macroscopic	Growth was very slow. A flat rather smooth colony with a fringe of aerial mycelium around the edge developed.	The colony was dark olive-green with a grayish nap. It presented zones, but they are not apparent in the photograph.
Microscopic	Mounts prepared from a giant colony, 1 month old, showed yeastlike spores in groups along the side of a segmented mycelium and also at the tip.	Numerous dark-brownish, yeastlike spores appeared in groups along the mycelia and at the tips.

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owing largely to its acid reaction, for which lactic acid is mainly responsible. Evaporation of such sweat on the surface of the skin or elsewhere tends to lower the pH and to increase the concentration of lactic acid so that the sweat becomes much more effective in this regard.

Tests on incubation of sweat show, however, that there is also a tendency for the sweat to become alkalinized owing to formation of ammonia by bacteria from the urea present. On the other hand, ammonia is more volatile than lactic acid, so that on evaporation much of it is lost and much of the lactic acid is regained. The volatile fatty acids are largely if not entirely formed on the surface of the skin by bacterial action on the lactic acid. Above pH 5.3 lactic acid is so completely ionized that few undissociated molecules of acid — on which much of the antibacterial action of the acid must depend — are present. The chief protective value of this acid lies, therefore, below pH 5.3. The volatile acids are less dissociated, and hence more effective, in the pH range of 5.3 to 6.2. Their most important role thus appears to be the extension of some degree of acid protection into these higher pH levels, which under certain conditions exist also on the skin.

Sweat is therefore capable of having quite diverse actions toward fungi, depending largely on the degree of evaporation that takes place. This parallels events in a solution of sugar; the diluted material can be attacked by fungi, whereas the concentrated material cannot. The changes in acidity or alkalinity are of course also important in determining the action of sweat on the fungi.

In the present experiments, sweat was obtained by encasing the subjects as far as their necks in a rubber bag while they were seated in a heat cabinet. Incandescent lamps furnished sufficient heat to obtain from 100 to 200 cc. of sweat in twenty to thirty minutes. Collected material was passed through a Berkefeld or Seitz filter, and control samples of filtered sweat were observed for sterility. Tubes of freshly filtered sweat were inoculated with the fungi. A solid medium was also prepared and used in Petri dishes in the usual manner. This medium was made by autoclaving a 4 per cent solution of agar at 15 pounds' pressure for twenty minutes. Four cubic centimeters of autoclaved agar solution was added to 6 cc. of sterile sweat, which had previously been heated to 50° C., and the mixture was poured into a sterile Petri dish. The material solidified and appeared like other agar media. The tubes of sweat and Petri-dish preparations were inoculated with fungi — *Trichophyton purpureum*, *Trich. gypseum*, *Microsporon gypseum* and Hormodendrum species — obtained from patients with cutaneous infections.

Transfers from the first cultures prepared in sweat were made to sweat-agar Petri dishes in order to obtain giant colonies. It was necessary to make transfers approximately three times to fresh dishes during the course of the work, because contaminants had entered the original dishes during the long incubation period and the latter were therefore unsuitable for the taking of photographs. Colony growth was the same each time, and no pleomorphism was observed. One-month-old cultures were used in all

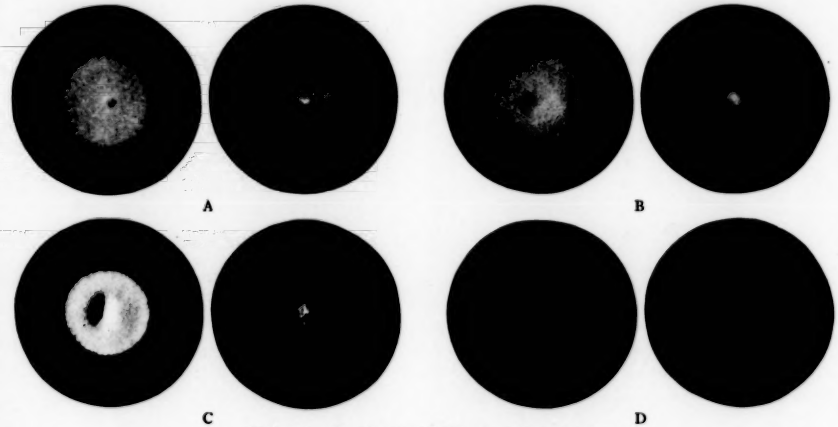

FIGURE 1. *One-Month-Old Cultures on Sweat Agar.*

The cultures on the left are on Sabouraud's medium, and those on the right are sweat agar. A — Trichophyton purpureum; B — Trichophyton gypseum; C — Microsporon gypseum; D — *Hormodendrum species.*

cases for the photographs (Fig. 1) and descriptions (Table 1).

For the tube cultures, transfers were made of each fungus to tubes of sweat that had been previously filtered through a Seitz filter and allowed to incubate at room temperature. Growth was slow in starting but grew well after the initial lag. Considerable evaporation had taken place after one month, so subcultures were made to a second series of sweat tubes. These subcultures grew more rapidly than the initial ones did. The photograph (Fig. 2) shows these tubes after an incubation period of one month. The cultural characteristics are given in Table 2.

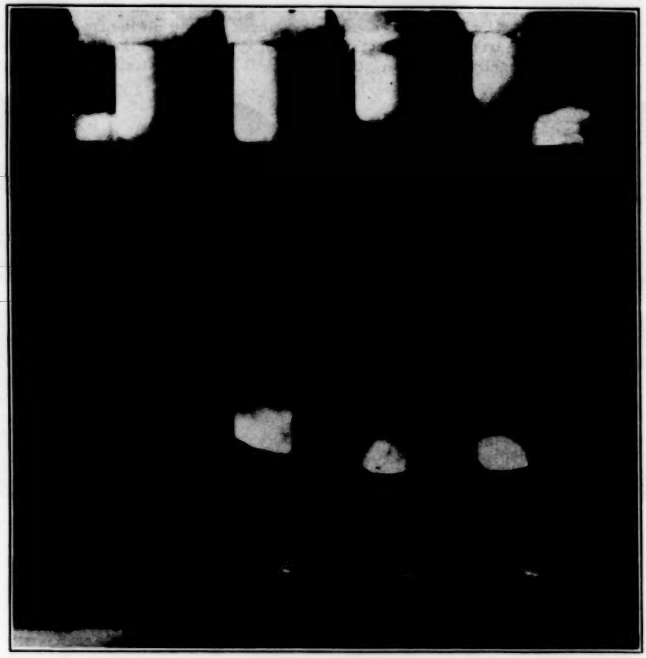

FIGURE 2. *One-Month-Old Cultures in Sweat.*

Starting at the left, the cultures are, respectively, as follows: Hormodendrum species; Microsporon gypseum; Trichophyton purpureum; *and* Trich. gypseum.

TABLE 2. *Description of Tube Cultures.*

Trichophyton purpureum. The fungus grew slowly and was white and velvety on the surface of the liquid. There was also a small amount of growth at the bottom of the tube.
Trichophyton gypseum. The fungus grew slowly and was white and velvety on the surface of the liquid. No growth took place at the bottom of the tube.
Microsporum gypseum. The fungus grew rapidly, producing a white, felty mycelial growth about 1 cm. in height on the surface. There was a small amount of growth at the bottom of the tube.
Hormodendrum species. The fungus grew very slowly, and there was more growth at the bottom of the tube than at the top. Mycelial growth was below the surface, while the surface growth was smooth and leathery.

DISCUSSION

The superficial fungus infections of the skin take place within or on the keratin layer. It is well known that keratin and related products serve well for the growth of fungi; thus, they are found growing on feathers and leather. Keratin is rich in sulfur-containing amino acids, and this raises the question of the relation of this element to fungus growth. If the sulfur is a requirement for the thriving of fungi, it must be present in such a form as not to lead to the production of sulfides. Cornbleet and Bergeim[4] have found that fungi are extremely sensitive to hydrogen sulfide and are killed or prevented from growing by extremely small concentrations.

Fungi also need moisture for growth and this is furnished by the sweat, but sweat alone can support

the growth of fungi, as shown in the above observations. Just what factor in sweat is the chief support of growth cannot be said. There are lactic acid and also volatile fatty acids. Some observers[5] have found sugar in sweat, although this conclusion may have resulted from the presence of reducing substances. There are sulfur-containing substances, although cultures of the hyphomycetes in sweat that were tested did not contain hydrogen sulfide. The same mediums, however, used for growing a number of varieties of bacteria did contain it.

So far as can be seen at the present, this study cannot be put to practical use. It may be that sweat mediums will be found to be useful for the differentiation of certain species that is difficult by other means. Such capacity was not shown in this study, but only a few varieties of fungi were used. No pleomorphism was shown for any of the cultures in three months of observation, so that they are fairly stable on these mediums.

Summary

A description is given of several fungi that were grown on sweat and a medium made of sweat and agar.

The role of sweat as an antiseptic and as a nutritive source is briefly reviewed.

Certain aspects of the natural growth of the hyphomycetes on the skin are considered, and the relation of some constituents in sweat to this growth are discussed.

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MEDICAL PROGRESS

GYNECOLOGY: CARCINOMA OF THE CERVIX (Concluded)

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THE series of cases reported in Table 1 have been classified by the League of Nations method and are from clinics large enough to have a sufficient number of cases to be significant. These results have been accepted by the Health Organization of the League of Nations and have been analyzed by Heyman.[30] They show how little variation there is from class to class and from total to total. There is no single way to treat cervical cancer, and Miller's[32] remarks, quoted at the beginning of this paper, cannot be better proved than by these results. It will be seen that the widest variation is in the Class III cases, and here is the greatest chance for errors in diagnosis, for some of these patients may have had only inflammatory nodes or masses and not cancerous masses, and thus an advanced case may have been reported as cured. If one could eliminate the Class III cases, there would be a close consistency of results. This discrepancy is probably due to incorrect evaluation, possibly to a better method of treatment.

In the surgical cases, Bonney's[27] curability of 40 per cent of those operated on is the only figure of consequence available.

Prognosis

A prognosis cannot be made from a study of microscopic slides alone. Since slowly growing tumors may be radioresistant and since rapidly growing tumors may respond but metastasize rapidly, it is the cases with a moderate grade of malignancy that do best. Early cases do better than late ones. Cases with distant metastases have a high mortality. If a patient has symptoms for more than six months, she is usually in the inoperative and incurable group. Goldscheider[34] believes that pyrexia in the course of x-ray treatment is an unfavorable sign. In order to evaluate the results of a method of treatment in a shorter time than five years, Meigs and Jaffe[35] were able to show that if 10 per cent is deducted from the three-year survivals for the fourth year and 5 per cent for the fifth year, the five-year end results can be estimated. Warren, Meigs, Severance and Jaffe[36] showed in a study of biopsy material taken before, during and after combined radium and x-ray treatment that if a tumor does not respond to treatment, as shown by destruction of cells, abnormal mitoses and an increase in connective tissue, the outlook is usually fatal. Nilsson[37] believes that the prognosis in cases of adenocarcinoma of the cervix is not so favorable as that in squamous-cell cancer, but his findings are not borne out by other authors.

Complications

The complications of cervical cancer that are due to its growth alone are destruction of the bladder and rectum and blockage of the ureters. Later in the progress of the disease hemorrhage and distant metastases to vital organs occur.

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Vesicovaginal fistula and rectovaginal fistula in untreated cervical cancer are not rare. Smith[38] believes that fistulas are twice as frequent in untreated cases as in treated ones and that they are evidence of advanced disease. He estimates the incidence of rectovaginal fistula as in 75 cases, that of vesicovaginal fistula as 1 in 92 cases and a combination of both as 1 in 129 cases. Death in untreated cases is often due to ureteral block and uremia. If it is desired to stop severe hemorrhage from a cervical cancer because of the favorable aspect of the cases with serious bowel injury, comprising about 2 per cent of the total number of cases treated. This injury is probably a small price to pay in the treatment of this disease, but it may indicate that too heavy treatment with the x-ray machine is being used. It is also true, however, that the same injury may occur with radium alone. Wigby[44] in 1943 reported some reaction in the sigmoid in 24 out of 100 patients. The injuries included hyperemia and edema, ulceration and bleeding, edema and pain, and obstruction. Pyometrium, peritonitis, pelvic

TABLE 1. *Analysis of Results of Treatment for Carcinoma of the Cervix.*

INSTITUTION	STAGE I		STAGE II		STAGE III		STAGE IV		ALL STAGES	
	NO. OF CASES	PERCENT. CURED	NO. OF CASES	PERCENT. CURED	NO. OF CASES	PERCENT. CURED	NO. OF CASES	PERCENT. CURED	NO. OF CASES	PERCENT. CURED
Memorial Hospital (New York City)	17	52.9	15	46.7	74	18.9	30	10.0	136	24.3
Woman's Hospital (New York City)	9	55.5	24	25.0	18	16.7			51	27.3
University of Brussels (Brussels)	6	33.3	20	40.0	28	14.3	9	0.0	63	22.2
Liverpool Radium Institute (Liverpool)	8	62.5	28	25.0	43	14.0	15	0.0	94	19.1
Marie Curie Institute (Paris)	9	66.6	20	60.0	75	30.7	22	4.5	126	33.3
Radium Center (London)	4	25.0	27	11.1	37	18.9	19	0.0	87	12.6
Institut du Cancer (Paris)	9	44.4	15	53.3	40	35.0	19	10.5	83	33.7
Institut du Radium (Paris)	12	66.6	44	43.2	34	32.3	12	8.3	102	38.2
Radium hemmet (Stockholm)	31	48.4	67	26.9	71	8.5	42	9.5	221	20.4
All reporting hospitals	607	55.2	1626	36.3	2417	21.2	1020	5.3	5672	26.3

growth, Leventhal, Lash and Grossman[39] advise extraperitoneal ligation of the hypogastric arteries. This should not be difficult to accomplish.

Ureteral block is not uncommon. Graves, Kickham and Nathanson[40] reported from the Pondville Hospital that 70 per cent of their cases had obstruction of the ureters and that complete urologic investigation was necessary. Also reporting from this hospital, Jaffe, Meigs, Graves and Kickham[41] state their belief that management of the obstructed ureters by means of nephrostomy frequently saves the kidneys. Treatment is omitted while the temperature is high and is resumed after nephrostomy has allowed it to return to normal. After the edema has subsided and cancer has been destroyed, the ureter may function normally. It was due to the above investigations at the Pondville Hospital that the Urologic Clinic dealing with the urologic complications of cervical cancer was established there.

Bowel injury following radiation treatment is not infrequent. Jones,[42] and later Aldridge,[43] have reported a series of serious injuries to the bowel by x-ray treatment. Jones describes severe injuries in 7 of 520 treated cases. In 5 of these the large intestine was affected, and in 2 the small intestine. Aldridge thinks that in many cases sufficient radiation to cure the patient cannot be given without damage to the intestinal tract. A great many of the manifestations of bowel injury, such as diarrhea, tenesmus and bleeding, are simple, but at a subsequent time — from months to years later — cicatrization may occur, with damage to the small or large intestine, necessitating colostomy to allow the bowel to heal or hemorrhage to cease, or even resection of the small or large bowel for obstruction. From the clinics at the Massachusetts General Hospital and Pondville Hospital I have collected 47 inflammation and so forth may follow combined radium and x-ray treatment. Philipp[45] and later Miller and Folsome[46] have reported fractures of the neck of the femur following radiation treatment for cervical cancer. This has led to the elimination of the lateral portal for treatment in some clinics. Martin[47] recognizes the danger of radiation and has tried to prevent untoward reactions. He has substituted multiple sources of radium of moderate intensity and frequently shifts containers of high intensity. He increases the distance for vaginal applicators by means of vaginal packs. He changes the packs frequently, uses no radon implants, avoids the ureters and employs intensive x-ray treatment only in advanced cases. He has elevated the lateral portals of treatment and gives his therapy in one careful series. He also allows a long interval between x-ray treatment and radium treatment. With all these measures I cannot agree, but the steps Martin is taking show that he has encountered difficulties, as have all clinics, and is searching for a way out of them.

CAUSES OF DEATH

The cause of death in most patients with cancer of the cervix is interference with the urinary tract, blocking of the ureters and uremia. Hemorrhage is a not infrequent complication, and large fatal ones due to erosion of a large artery are not uncommon. Many patients with cancer of all kinds die of persistent depletion due to loss of weight, lack of appetite, obstruction of the bowels, pyrexia and so forth.

PREVENTION

Improvement in the methods of reconstruction of cervical injuries comprises one means for the prevention of cervical cancer. The use of office cautery

and repair or operation on the cervix will surely aid in avoiding cancer, but even perfect repair or perfect reconstruction will not prevent it if all the cancer-producing factors are present. It is not known how long it takes malignant disease to develop, how it starts or from what sort of tissue it arises.

The best method of prevention is excision, and the only type of excision that completely removes the cervix is total hysterectomy. This cannot always be advocated, but with the decreasing mortality from this operation it is probable that the number of unsuspected cervical cancers found in the laboratory will approximate the number of deaths from the operation. No one can advocate removal of the uterus and cervix in every married woman over the age of thirty, but one can properly advise, if for any reason abdominal operation is necessary, not that repair, cauterization and amputation be done but that the uterus and cervix be completely removed. This can be called radical advice, but to one who has seen cervical cancer develop in 2 cases after cauterization and supravaginal hysterectomy it does not seem at all radical. If total hysterectomy cannot be done with so low a mortality as supravaginal hysterectomy, each case should be sent to someone who can do it. A discussion of cancer of the cervical stump will be given later.

Schmitz,[48] Macfarlane et al.[49] and Phaneuf and Belson[50] advise observation of the cervix. Schmitz says that this should be made once a year; Macfarlane, who examined 1000 women, says twice a year; and Phaneuf and Belson biopsied 100 consecutive patients. Macfarlane et al. found 4 cases, and Phaneuf and Belson also found 4 cases. The early recognition of cancer is so difficult that in any suspicious case it is much safer to remove the cervix than to leave it, and total hysterectomy is the best method of prevention.

Von Graff[51] found that cancer of the body of the uterus was nine times as frequent and cancer of the cervix four times as frequent in patients with fibroids as in those with a normal uterus, so that in such cases total hysterectomy is the procedure of choice.

Premalignant Lesions and Very Early Cancer

The question of premalignant lesions is a much disputed one, and it is not yet clear what part epidermidalization and squamous-cell metaplasia play in the development of cancer of the cervix. Knight[52] in reporting 17 cases of superficial epithelioma states that cancer occurs not infrequently in tissue that has undergone squamous-cell metaplasia. He believes that the latter may be important and may be the early phase of intraepithelial cancer. Mezer[53] in a careful study of 1636 cases of polyp found 5 with cancer; in all of them the polyps were associated with squamous-cell metaplasia. It is doubtful that the time has yet come when total hysterectomy can be advocated by the pathologist because of the finding of epidermidalization and squamous-cell metaplasia, for such conditions have been seen in patients who have been followed for many years after the diagnosis was made. Nevertheless, it is also obvious that such a condition cannot be overlooked and that a careful follow-up for years is essential.

The question of cancer in situ, or intraepithelial or preinvasive cancer, is also not yet decided, but it is recognized by such an authority as Meyer[54] as being carcinoma. The experience of many is that if cancer in situ is present in a biopsy specimen, there may be invasive cancer in some other area in the cervix. Investigations at the Pondville Hospital indicate that the diagnosis of preinvasive cancer indicates that more biopsies should be made of various areas in the cervix. Thus, all but one of the preinvasive lesions were found to be true invasive cancer. Perhaps all that needs to be done for patients with preinvasive cancer is a total hysterectomy, but inasmuch as cure depends on radical removal, the Wertheim operation is not out of place. Schiller[55] and also Stevenson and Scipiades[56] believe that early cancer grows slowly. The latter followed a woman with preinvasive cancer for eight years and one month, and the cancer finally became invasive. Another patient was followed for three years, and after death, serial sections of the cervix showed invasive cancer. It is probable that cancer in situ or preinvasive cancer cannot be considered as Bowen's disease, for that lesion remains intraepithelial. Knight[52] states that it is not much like Bowen's disease. The use of radium in very early preinvasive cancer may be sufficient. Amputation of the cervix is not sufficient, for it does not remove all the endocervical epithelium. Total hysterectomy is therefore best; yet, as most cases show invasive cancer, perhaps the more radical Wertheim method should be advised.

To sum up, changes in the type of cervical epithelium are probably due to inflammation, yet it is not at all certain that such changes are not part of the picture of malignant change. Cancer in situ must be regarded in the light of our experience as early cancer, and the proper treatment is either full radium or x-ray treatment or total hysterectomy, or, even better, the Wertheim operation.

Cancer of Cervix after Supravaginal Hysterectomy

This problem of cancer of the cervix after supravaginal hysterectomy is a real one, and anyone seeing large numbers of cervical cancers is struck by the great number of such cases. These cases are of two kinds, those in which the operation is done at the time the cervical cancer is present, and those in which the cancer develops some years later. I have had under my supervision at one time 3 patients in whom supravaginal hysterectomy had been done when they had obvious cervical cancer. This is inexcusable and is due to lack of inspection and ex-

amination of the cervix at the time of operation. It is probable that these patients were bleeding and had fibroids, and that the abdominal operation was done and the uterus removed without preliminary inspection of the cervix in the lithotomy position. In other cases the cancer develops within three to six months postoperatively and was certainly present at the time of the operation, but was not recognized because it was so early or was present in the endocervix. This type of mistake is more excusable than the former, but in either, if the patient had had a total hysterectomy instead of a supravaginal hysterectomy, the results might have been better. In still other patients the tumor occurs from two to twenty-five years after the operation. It is pathetic to see such patients, for they believe that when they were operated on the uterus was removed. Surgeons leave the cervix behind because of the danger of morbidity, because of the possibility of interfering with sex activity and because they fear the more difficult operation.

With the advances in the knowledge of the operation and better preparation of the patient for it, there is no excuse for not removing the cervix. In certain cases — in bad-risk patients and in obviously difficult operations — the cervix may be left, but this should be the great exception and not the rule. In 1934, Gellhorn and Spain[57] stated that the danger of total hysterectomy is far less than that of cancer of the cervical stump. Von Graff,[51] who reported 581 cases of this disease, believes that in 137 cases (23.5 per cent) it was present at the time of the operation and that the remaining cases would have been cured by total hysterectomy. He condemns "coning out" the cervix as not being sufficient treatment, since it leaves the squamous-cell epithelium on the outside of the cervix. Behney[58] believes that the chance of curing cancer of the cervical stump with radium is no less than that in corresponding classes of cervical cancer with the uterus left intact. Ward[59] agrees with his conclusions. It is the experience of our clinics that the treatment is not so efficacious because the canal of the cervix cannot be used as the source of the central radium applicator. The danger of fistulas, as all agree, is greater because the protection of the uterus is absent. It has been the custom in some clinics to do a vaginal cervicectomy in early cases of cancer of the cervical stump, and good results have been obtained, but if surgery is to be done in early cases, whether in the cervical stump or in the untouched uterus, the Wertheim operation with its radical removal of nodes and vaginal tissue is the procedure of choice. The percentage of cancer of the cervical stump among cervical cancers is 3 to 4 per cent in all clinics, — not a very great number, — but at the Pondville Hospital there have been over 100 cases. The sad thing about these cases is that if the total operation had been done, no patient would have developed cancer.

Relief of Pain

The treatment of pain in cervical cancer is usually limited to patients with advanced disease who are not likely to be cured. Cleanliness, frequent douching, changing of dressings and bed rest help a great deal. The use of acetylsalicylic acid (aspirin), codeine and narcotics is familiar to all, yet there are patients whose pain cannot be controlled by ordinary measures.

Sometimes x-ray treatment distributed over the area of pressure and invasion by the tumor is of value. There are, however, many advocates of the use of intrathecal injections of absolute alcohol (Todd[60]). This method is undoubtedly satisfactory in some cases, but in the great majority if sufficient alcohol is injected to stop pain, some sort of interference with the function of the bladder and rectal sphincter takes place and weakness of the legs occurs. The length of the relief from pain varies from a few hours to a few months. Certainly in hopeless cases this method can be tried, but no guarantee can be made that the patient will obtain a satisfactory result.

The use of sympathectomy for control of pain has been advocated by Todd, who does a presacral sympathectomy. Others, among them Waterman,[61] have reported success with this type of operation. Relief can be obtained from pain in the midline, but in most cases it is not satisfactory. Chordotomy has distinct possibilities, and unilateral or bilateral section of the arterolateral columns is not an extremely formidable operation and may be carried out under local anesthesia. These patients lose the sense of pain and temperature but not that of touch; they are not paralyzed. In patients with severe pain and with not too advanced cancer who appear to be going to live for months this operation offers a great deal, but for patients who are near demise alcohol injections are just as efficacious. The trouble with the operation is that it is usually done when the patient is in extremis and is shortly followed by death. Its use in earlier cases gives results that are more satisfactory. The danger of interfering with the bladder and rectal sphincter is a real one, but the relief of pain in hopeless cases is well worth the risk.

Cancer of Cervix in Nulliparas

Nulliparas constitute a fairly high percentage — from 5 to 12 per cent — of patients with cancer of the cervix. It is often impossible to state whether a married nullipara has ever miscarried, and in the unmarried patient the question of whether a pregnancy has occurred is often a difficult one to ask. Since cancer of the cervix does occur in nulliparas, pregnancy or labor is not essential for the development of the disease. Nulliparas may have had endocervicitis before the development of cancer and may have had an exposed endocervix, with irritation. The knowledge that cancer is not too

infrequent in nulliparas is important, so that a surgeon will not content himself with doing a supravaginal operation merely because the patient has had no children. Careful inspection of the cervix must be done before a supravaginal operation, and its removal with the uterus is far better. Inasmuch as many nulliparas have fibroids, and since cancer of the cervix is more frequent in patients with fibroids than in those with a normal uterus, removal of the cervix in such cases is essential.

Cancer of Cervix in Pregnancy

Keller[62] reports 3 cases of cancer of the cervix among 4000 pregnant women. The patients had no symptoms, the tumor being discovered at biopsy. Danforth[63] found the frequency during pregnancy to be 0.03 per cent. There is no agreement whether pregnancy causes an abnormal rate of growth of the cancer. Miller[64] believes that it does, but quotes Wagner, Weibel, Meyer, Schweizer and others who believe that it has a retarding influence. Smith[65] states that pregnancy is detrimental to patients with unarrested malignant tumors. He thinks that the tumor growth may be retarded by the pregnancy but that it is accelerated afterward.

The mode of treatment of cancer of the cervix in the pregnant woman must be decided according to the size of the conceptus. . . . Keller[62] agrees with Brouha and Gosselin[66] that in the first half of pregnancy a hysterectomy should be done in operable cases and that radium should be given in inoperable ones. They advise against x-ray treatment in the first half because of its deleterious effect on the fetus. They believe that in the second half radium is ideal and has but little effect on the fetus. They allow the pregnancy to go to term and do a cesarean section. Danforth[63] believes that labor may be dangerous and is occasionally impossible, and advises x-ray and radium at once when the pregnancy is far enough advanced to allow viability. He advises termination of the pregnancy if full treatment is given, because of the danger to the child. Brouha and Gosselin[66] analyzed 39 cases, including 2 of their own. In 10 cases radium was given in the first half of pregnancy, and in 7 an interruption of the pregnancy occurred in one to five and a half months. Three patients went to term and gave birth to normal children. Twenty-nine had radium, in the second half of pregnancy, and in this group there were 6 miscarriages and 2 fetal abnormalities. Eight of the mothers treated in the first half of pregnancy died. Of those treated in the second half of pregnancy, 19 were traced and 9 were living and well. These writers conclude that since irradiation in the first half of pregnancy is dangerous to both mother and child, a hysterectomy should be done. In the second half radium should be given, and if a miscarriage occurs a hysterectomy should be done at once. Hurdon[67] gives the incidence of cancer of the cervix in pregnancy as 0.5 to 2.0 per cent. In her clinic the percentage was 0.6 per cent. She cites Pankow as collecting 50 cases of carcinoma during pregnancy that he had operated on with a five-year survival rate of 42 per cent. Hurdon believes that the uterus should be emptied because spontaneous abortion occurs two to four weeks after radiation without complications. She warns of the possibility of injury to the germ plasm of the child whose mother's cervical cancer has been irradiated. She states that there may be danger of transmitting germ-plasm defects. On the other hand, there are children who have been delivered following irradiation of their mothers who have arrived at school age without any apparent physical defect. Hurdon's summary of the treatment of cancer of the uterus complicating pregnancy is excellent, and is presented below:

If the cancer is discovered during pregnancy:

If the cancer is operable, and the child not viable:

Radical excision (Wertheim) *of the unopened uterus.* The prognosis for the mother is comparatively good.

Radium therapy. If not followed by abortion, evacuate by abdominal hysterotomy, or the child may go to viability and be delivered by cesarean section. The prognosis for the mother is favorable. Abortion usually follows, and abnormalities are frequent among the children that survive.

If the cancer is operable, and the child viable:

Cesarean section followed by Wertheim's operation. The prognosis for the mother is unfavorable; there is a good chance of survival for the child.

Radium therapy preceded or followed by Cesarean section (according to the period of gestation). The prognosis for both mother and child is comparatively favorable.

If the cancer is inoperable, and the child not viable:

Radium therapy followed by delivery by abdominal hysterotomy (in accordance with religious principles, pregnancy may be allowed to continue, with delivery by cesarean section at or near term).

If the cancer is inoperable, and the child viable:

Radium therapy preceded or followed by cesarean section (according to the period of gestation).

If the cancer is discovered at the time of labor, and the baby is alive:

If the cancer is operable:

If the presenting part is still in the uterus:
cesarean section followed by Wertheim's operation.

If the presenting part is through the cervix:

Labor followed by radiation treatment (as soon as involution permits). Treatment may be begun by x-ray therapy a few days after delivery, and intracavitary radium as soon as practicable. The beginning of treatment should not be delayed beyond the ninth or tenth day.

If the cancer is inoperable:

If the presenting part in the uterus:
Cesarean section followed by radiation therapy.

If the presenting part is through the cervix:

Labor followed by radiation therapy (as soon as involution permits).

The following criticism of Hurdon's advice should be made: If the cancer is operable and the child viable, it is perhaps better to do a cesarean section and then give radium to the cervix, and six weeks later to operate by the Wertheim method. The huge veins, the large lymphatics, the soft tis-

sues and the obvious danger of the infected cervix suggest treatment with radium, sterilization of the cervix by radiation and later operation. In cancer discovered at the time of labor, radical surgery should not be done for cervical cancer at the same time as cesarean section, for the reasons given above. There have been 3 such cases in our clinics. The first patient, who had been pregnant for six months, was given radium. A cesarean section was done at eight months; then x-ray therapy was given and radium treatment was repeated. The patient died of extensive miliary metastases one year after treatment. The second patient was given radium in the sixth month of pregnancy and had a cesarean section in the eighth month. The baby died of hemorrhagic disease of the newborn, and the mother was given further radiation and has been alive and well for over five years. The third patient was six-months pregnant, with an early growth. She was given radium in the cervix, a cesarean section was performed six weeks later, and three months after that a Wertheim hysterectomy was performed. The patient is alive but has a ureteral fistula, which means later nephrectomy. She had no metastases in the lymph nodes and should do well. A transverse cervical cesarean section had been done, and this interfered with the dissection about the cervix at time of the Wertheim operation. In another such case, it would seem wiser to do the classic operation rather than the cervical.

Hurdon discusses 15 cases of pregnancy subsequent to involvement of the cervix with cancer. Spontaneous delivery occurred in 8 cases, and 1 patient was delivered by cesarean section. Abortions were induced in 2 cases, and were spontaneous in 3. One patient had three abortions before a normal child was born. One child was delivered by morcellation. All the living children were said to be healthy, both physically and mentally. There are no records of a second generation.

Summary

The treatment of cancer of the cervix by radiation is at a standstill. Radium alone and combined with x-ray has given excellent results. It is now time to concentrate on early diagnosis by means of the vaginal smear, the colposcope and the Schiller test. The addition of surgical removal of the lymph nodes and the radical Wertheim's operation in favorable cases may produce better results.

Cervical cancer can be prevented only by total removal of the cervix by total hysterectomy when it is irritated, lacerated or suspicious.

Various problems of cervical cancer are discussed.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

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CASE 30201

PRESENTATION OF CASE

A twelve-year-old mongolian girl entered the hospital because of vomiting and fever.

The patient was normally delivered at full term. The parents were normal. Development was slow, and she presented such a feeding problem that, at three, she was a seriously malnourished child. Dentition started at eight months, walking at nineteen months and talking at three years. She had measles and whooping cough as a child. At the age of six a diagnosis of mongolism was made, and about three years later she was placed in an institution. During the first year there she had recurrent ulcerations of the mouth, from which smears occasionally showed Vincent's organism. In the following two winters she had occasional episodes of "stomach upset," with vomiting and diarrhea for several days. These cleared with a special diet. She remained in essentially good health until 4:00 a.m. on the day before admission, when she suddenly started to vomit. The vomiting was "explosive," and continued during the day; the vomitus consisted of "white curdy and buttery masses, stool-like, with no bile." There was slight watery diarrhea, which stopped by mid-afternoon of that day. Tenderness was elicited in the "lower intestine." The abdomen became distended. She developed fever and the white-cell count was 29,200, with 82 per cent neutrophils. The red-cell count was 3,840,000. She continued to vomit occasionally during the following night but was slightly more comfortable on the morning of admission. Distention of the abdomen and tenderness became marked, especially on the right. She was transferred to this hospital.

Physical examination showed a slightly cyanotic, underdeveloped, typical mongolian girl. The heart and lungs were negative. The abdomen was distended and tympanitic. Peristalsis seemed to be depressed, and infrequent high-pitched sounds were heard. The liver was two fingerbreadths below the costal margin. The spleen was not enlarged. There was spasm on the left side of the abdomen. It was difficult to judge tenderness, but on one occasion the patient shrieked bitterly on deep palpation in the right lower quadrant. There were no masses. Rectal examination was negative.

The blood pressure was 155 systolic, 120 diastolic. The temperature was 101°F., the pulse 160, and the respirations 40.

FIGURE 1. *Photomicrograph of Kidney.*

*On leave of absence.

Examination of the blood showed a white-cell count of 28,000. The urine contained occasional white cells, but was otherwise negative.

During the examination she became completely unresponsive and began to show peculiar gyrating motions of the arms. She became cyanotic, with an unusual mottled distribution. Rapid epileptiform convulsions began and persisted in varying degrees of severity for one hour. She was given 1 gm. of sodium phenobarbital and 10 cc. of paraldehyde. A lumbar puncture at the end of this time showed clear fluid, which contained 6 lymphocytes per cubic millimeter; the Pandy test was negative. Following this, she became irritable and irrational, thrashed about the bed and required restraint; 12 cc. of paraldehyde was given. About one hour later she suddenly threw herself on her face and vomited a slight amount of brownish material. The pulse was irregular, with a rate of 30. Three minutes later, three hours after entry, no heart beat could be heard.

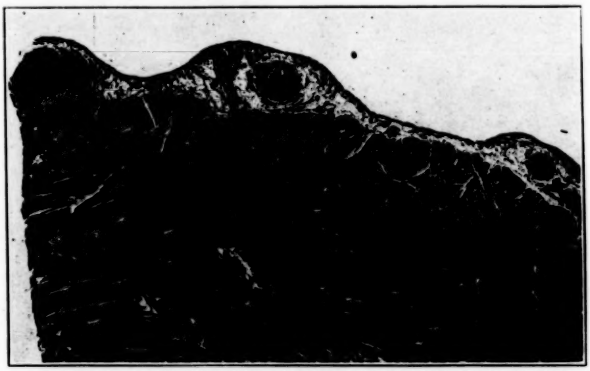

FIGURE 2. *Photomicrograph of Heart.*

DIFFERENTIAL DIAGNOSIS

DR. ROBERT R. LINTON: We have here a typically mongoloid individual who entered the hospital because of an abdominal condition. Diagnosis is most difficult, since we have little if any evidence except the clinical examination and a very short history. In view of the high white-cell count one should consider an inflammatory condition, perhaps something that was obstructing the blood supply of the bowel, with secondary infection resulting from it. I believe, but I do not know, that congenital anomalies are not infrequently found in this condition. So one has to consider some of the congenital conditions that might produce vomiting, abdominal pain and distention and a high white-cell count. The temperature was 101°F. on one occasion.

I thought of the possibility of malrotation, with twisting and intestinal obstruction as a result. Most cases of malrotation, however, are seen relatively early in life, and it would be unlikely for a patient to reach the age of twelve and suddenly to develop such a condition. The only one that I can think of is a volvulus of the cecum and ascending colon, which I do not see how I can rule out.

Are there any x-ray films of the abdomen?

DR. BENJAMIN CASTLEMAN: No.

DR. LINTON: Another condition that should be considered is reduplication of the intestinal tract, which gives signs of intestinal obstruction; again, I cannot rule this in or out. One also has to consider a Meckel's diverticulum, which might produce intestinal obstruction owing to strangulation of the bowel around a fibrous band extending from the end of the diverticulum to the abdominal wall. Intussusception is also something that one should consider, but I think that it can be ruled out, since 75 per cent of the cases of intussusception appear before the age of one. Another condition is an intra-abdominal herniation, as well as other congenital conditions that arise in the abdominal cavity.

I also thought of a peptic ulcer. Peptic ulcers with perforation do occur in children, but in view of the essentially negative past history I do not see how I can make a diagnosis of peptic ulcer.

There is another condition that I cannot rule out — appendicitis. The only thing against appendicitis is the sudden onset with an explosive type of vomiting, which is a peculiar way for appendicitis to manifest itself.

After running through the various possibilities I cannot make a definite diagnosis. I believe the likeliest was a volvulus of some portion of the intestine, interference of the blood supply, intestinal obstruction and peritonitis. The sudden death I

cannot explain unless the child — in spite of the fact that the physical examination was negative — had a congenital cardiac lesion, which again is a fairly frequent finding in cases of mongolism.

DR. CASTLEMAN: Dr. Gross, would you like to suggest a diagnosis?

DR. ROBERT E. GROSS: I am inclined to bet on the likeliest thing on the basis of statistical facts — appendicitis.

DR. CASTLEMAN: Dr. Butler, have you any comment to make on the fact that the patient had hypertension?

DR. ALLAN M. BUTLER: The blood-pressure reading was taken when the child was in a state of great excitement. I know of no other reason, not having seen the patient or knowing the exact circumstances under which the blood pressure was measured.

DR. LINTON: May I say that it struck me that the patient did have a high diastolic pressure, but I did not connect that with the cause of death.

DR. CLEMENS BENDA: The patient had a normal blood pressure some time before admission, but it was not measured during her acute illness.

I saw the child the night before she was admitted. At that time she was in acute distress. She vomited every few minutes. It was reported to me that she had been vomiting since morning, but it was difficult to find out the exact character of the vomitus. When I saw it, it was fecal. The belly was extremely distended and tender. My diagnosis at that time was complete obstruction due either to volvulus, to intussusception or to a ruptured appendix.

I was much interested to hear that the child went into convulsive seizures in the hospital. It may be mentioned that it is extremely rare for a mongolian to have convulsions. Of about 400 such patients whom I have seen, only 2 had epileptic seizures.

I should also like to mention another fact, although it is of no immediate interest for the diagnosis in this case. In two autopsies on mongolian children I found a microcolon, which is not mentioned in the literature. We hear and read frequently about megacolon, but the occurrence of a microcolon is apparently extremely rare. In the two cases in which I made this observation the transverse and descending colon was the size of a little finger, whereas the ascending colon had a normal lumen.

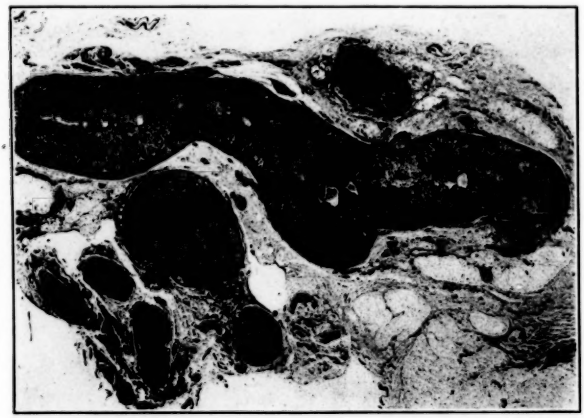

FIGURE 3. *Photomicrograph of Adrenal Gland.*

CLINICAL DIAGNOSES

Mongolism.
Gastroenteritis?
Intestinal obstruction?

DR. LINTON'S DIAGNOSIS

Volvulus of small intestine, with gangrene and peritonitis.

ANATOMICAL DIAGNOSES

Periarteritis nodosa, generalized.
Gangrene of small intestine.
Peritonitis, acute generalized.
Miliary infarcts of adrenal glands, liver and kidneys.
Bronchopneumonia.
Mongolism.

Pathological Discussion

Dr. Castleman: Autopsy showed about a liter of turbid, hemorrhagic fluid in the abdominal cavity. The small intestine appeared red and gangrenous, and at the time of autopsy we thought that it had twisted and a diagnosis of volvulus of the small bowel was made. Microscopic sections, however, showed something extremely interesting, which perhaps accounted for the gangrene of the bowel.

In sections of the kidneys practically all the blood vessels, especially the medium-sized arteries, were diseased (Fig. 1). Many showed marked intimal proliferation, with practically no lumen; others had tically complete destruction of the wall in some vessels (Fig. 4).

We have, then, a classic example of polyarteritis or periarteritis nodosa in a child of twelve, the youngest we have seen here. Involvement of the mesenteric vessels was the cause of the gangrene of the bowel. Lesions were found in practically every organ, including the brain, which may account for the convulsions.

Dr. Butler: How sure is Dr. Benda that the child's blood pressure was normal?

Dr. Benda: According to the record in 1941 the blood pressure was 120 systolic, 70 diastolic. For a

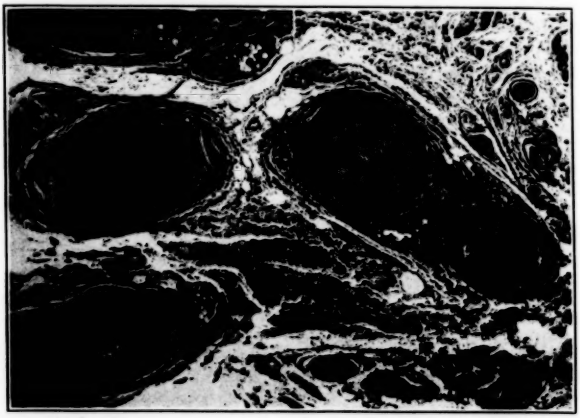

Figure 4. *Photomicrograph of Periadrenal Vessels.*

marked cellular infiltrations around them. These perivascular cells were polymorphonuclears, plasma cells and eosinophils. In sections stained for elastic tissue, it was obvious that part of the elastica was completely broken, with fibrinoid necrosis of the wall. The intimal proliferation was apparently secondary to the disease in the wall.

The liver showed exactly the same process, with involvement of practically every vessel. In sections of the heart the coronary arteries were almost completely occluded by fibrous tissue (Fig. 2). Throughout the myocardium there were small areas of degeneration.

In sections of the adrenal glands, the surrounding fat showed vessels in all stages of the disease (Fig. 3); at one of the poles there was a small infarct due to the vascular change. On higher magnification, the periadrenal vessels showed extreme arteritis of all layers and also fibrinoid necrosis, with prac-

mongolian that seems to me slightly elevated, since they usually have a systolic pressure not higher than 100.

Dr. Castleman: Have you seen this disease in children, Dr. Gross?

Dr. Gross: Dr. Butler probably remembers a case at the Children's Hospital that might be akin to this. The child was seven or eight years old and had marked arterial lesions, but not enough to give localized inflammation of the bowel and hypertension.

Addendum. Further inquiry into the patient's history after the diagnosis of periarteritis nodosa had been established disclosed that, twenty months before death, the patient had dysentery, for which she received over 600 gr. of sulfathiazole over a sixteen-day pe iod. The sulfathiazole blood level was under 6 mg. per 100 cc., except for one day when it reached 12.6 mg. The white-cell count was 20,000,

with 80 per cent neutrophils, and the red-cell count was about 4,000,000. Many face eruptions and multiple abscesses developed and continued to be present for the following two months. The diarrhea recurred four months later, when she was given a total of 135 gr. of sulfadiazine over a four-day period. At that time a positive culture for the Sonne type of dysentery was obtained. The cultures were negative one month later. Four months later, about one year preceding death, she received sulfadiazine for only one day, probably not more than 30 gr.

In view of Rich's[1,2] recent studies on the role played by sensitizing antigens, especially sulfonamides, in the production of periarteritis nodosa, it is not unlikely that the patient in this case, while under sulfonamide therapy, developed acute arterial lesions, which at autopsy a year later showed various stages of healing.

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CASE 30202

Presentation of Case

A fifty-seven-year-old housewife was brought into the hospital because of pain in the left upper quadrant.

The patient was in apparent good health until six hours before entry, at which time she fell from the piazza of her home to the ground, a drop of six feet. She apparently landed on her left side and experienced severe pain in the left upper quadrant and left shoulder. She was able to stand up, however, and walked into the house, but she did this with considerable effort because of the pain. After sitting down in the house for a few minutes she felt "shaky," and during the next two or three hours had three attacks of vomiting. What the vomitus consisted of was not noted. The vomiting and deep breathing increased the pain in the left upper quadrant. There was no pain in the chest, no loss of consciousness, no loss of blood from any orifice, and no bowel movement.

The past history was negative except for an admission into the hospital some months previously for drainage of a carbuncle of the neck.

Physical examination showed a well-developed, rather obese woman who was complaining of pain in the left upper quadrant. The heart and lungs were negative. There was tenderness on pressure over the lower ribs, but no crepitus, or pain on inspiration. Marked tenderness was elicited in the left upper and lower quadrants, but none in the costovertebral angles. A nontender, movable mass twice the size of a grapefruit was palpable in the left lower quadrant, which on pelvic examination seemed to arise from the left vault. This mass had been felt at the time of the previous admission.

The blood pressure was 100 systolic, 60 diastolic. The pulse was 70. The temperature and respirations were normal.

Examination of the blood showed a red-cell count of 4,560,000, with 80 per cent hemoglobin. The white-cell count was 24,000. The urine contained occasional white cells and innumerable red cells.

X-ray examination of the chest showed no evidence of fracture or pneumothorax. An intravenous pyelogram revealed the kidney outlines to be normal. The dye appeared in good concentration, outlining nondilated urinary passages, and no evidence of extravasation of dye into the soft tissue was seen. Plain films of the abdomen showed the pelvic mass already described.

Two abdominal taps were negative. The patient was given ⅛ gr. of morphine and ice packs over the left quadrant. In the course of the next few hours the blood pressure rose slowly and the pain subsided. She was kept under close observation. In the course of the next two days the shoulder pain completely disappeared and the tenderness in the left upper quadrant practically disappeared. She was voiding well, but the urinary sediment still contained 20 to 25 red cells. Bowel movements were normal, and there was no vomiting.

On the fourth hospital day she had minimal pain in the left leg, with some swelling about the medial aspect, and there was a slight transient rise of temperature, which subsided. The next day, examination was entirely negative except for the persistent mass in the pelvis. The urine was clear, and a gastrointestinal series was negative except for a small amount of fluid in the left costophrenic angle.

On the seventh hospital day an operation was performed.

Differential Diagnosis

Dr. Arthur W. Allen: Perhaps we might look at the x-ray films.

Dr. Milford Schulz: There is nothing here except that which is confirmatory of the statements in the protocol. This film of the abdomen demonstrates the mass rising above the iliac crest. The pyelogram shows good kidney function, and I see nothing to suggest damage to the kidney.

Dr. Allen: Does the mass change the course of the ureter in any way?

Dr. Schulz: It is difficult to say that it does not displace it anteriorly, but it does not displace it laterally, in so far as it can be traced.

Dr. Allen: Does the mass go into the pelvis?

Dr. Schulz: I cannot see the lower margin where it merges with the pelvic shadows. Its lowermost reaches cannot be definitely determined.

This film of the chest and ribs shows nothing unusual. The shadow of the spleen cannot be outlined.

DR. ALLEN: In the gastrointestinal series there is mention of a small amount of fluid in the left costophrenic angle. Can you point that out?

DR. SCHULZ: That probably was a fluoroscopic observation; it cannot be seen on these films with any degree of certainty.

DR. ALLEN: We assume that, at the time of this woman's first admission, a diagnosis was made regarding the pelvic tumor — that is, some note must have been made about it because it was recorded in the physical examination. It is not stated, however, whether she had been given a house appointment to have something done about it. I assume that she had been told that it would be a good idea to come back at least for examination and possibly to have this tumor removed. Obviously it was not considered to be malignant; otherwise she would have been followed and probably brought back to the hospital earlier.

We come down then to the present illness, which started with a fall, not from a great height to be sure, but far enough to cause considerable damage. The fact that she had pain in the left upper quadrant and pain on pressure over the lower ribs is consistent with the red cells found in the urine; in other words, she probably had a contusion of the kidney. The intravenous pyelogram rules out a serious injury to the kidney, because if the kidney itself had been fractured, there would have been some extravasated dye around the kidney when the pyelogram was made. The fact that she showed a considerable number of blood cells in the urine for three or four days after injury is, I believe, sufficient evidence to prove that she did have a contusion of the left kidney. It is difficult for me to connect the contusion of the kidney and the pelvic tumor, and I am going to assume that the two lesions had nothing to do with each other, that the accident did not produce a hematuria from the standpoint of the tumor, and that the pelvic tumor was an incidental finding and was not a factor in the acute illness.

Two interesting observations make one speculate about the region of the injury. One is the white-cell count of 24,000. I assume that that was repeated and confirmed. A contusion of the kidney will not give a white-cell count of that height, nor will a great many other acute injuries, except injury to the spleen. If a patient has had an abdominal injury and has a white-cell count above 20,000 — it is frequently above 30,000 — one must be suspicious of an injury to the spleen. We do occasionally pick up a high white-cell count associated with other acute conditions of the abdomen, particularly mesenteric thrombosis and pancreatitis. The other day a patient arrived here with typical appendicitis and a confirmed white-cell count of 27,000. That is very unusual. But the high white-cell count six hours following an injury in the region of the spleen makes one suspicious that, in addition to the contusion of the kidney, there might have been injury to the spleen.

There is another lead in the story that makes me think of the spleen. Obviously the residents who studied this patient thought of the possibility of intra-abdominal bleeding, because they tried twice to aspirate blood from the abdominal cavity, but both these attempts were unsuccessful and they quite rightly assumed that there was no intra-abdominal bleeding.

It is obvious from the record that, because of the high leukocyte count and the tenderness in the splenic region, they were suspicious that there might have been an injury to the spleen. Their suspicions were allayed, however, inasmuch as the patient got over her symptoms promptly and her white-cell count became lower.

It is quite possible, though, to have a fractured spleen that gives this picture at entry, the spleen having become tamponaded by omentum, so that there is a period of complete freedom of symptoms. We all know of a good many cases in which a fracture of the spleen temporarily stopped bleeding. A man injured on a football field, for instance, improves to such an extent that he is allowed to play a week later, only to have a burst of bleeding, at which time the correct diagnosis is usually made. A great many cases of delayed bleeding of the spleen have been recorded, particularly those by McIndoe*; and in one case a secondary hemorrhage occurred as late as twenty-eight days after the original injury. The other day in the ward I saw a boy of about twelve who had fallen on a picket fence on his left side five or six days prior to entry. At operation he had a well-tamponaded spleen, which was successfully removed. The spleen behaves differently from the other abdominal organs in that respect. Once hemorrhage has ceased from the liver, one can be reasonably sure that a secondary burst will not occur; but even though hemorrhage from the spleen has temporarily stopped, it is wiser to remove the spleen.

They do not tell us what operation was performed. I assume, however, that they did not explore this woman for the spleen. They probably assumed that all the trouble in the left upper quadrant was due to the contusion of the kidney. If the operation was done for the pelvic tumor and if they found no blood in the peritoneal cavity, they probably removed the pelvic tumor; but if they found blood, in spite of the two negative taps, they very likely investigated the spleen. If they found blood in the peritoneal cavity, I hazard the guess that they found the spleen fractured and tamponaded.

The diagnosis as I see it is a pelvic tumor of some sort. The patient was fifty-seven, which is between the age of fibroids, which occur most frequently in

*McIndoe, A. H. Delayed haemorrhage following traumatic rupture of spleen. *Brit. J. Surg.* 20:249-268, 1932.

the fourth decade of life, and that of ovarian cysts, which occur either early or late in life. I assume that the chance that this was a fibroid is better than that it was an ovarian cyst. In the acute condition she had a contusion of the left kidney with hemorrhage, and I raise the question of the possibility of a fractured spleen as well.

Clinical Diagnosis

Fibroid uterus or ovarian cyst?
Intra-abdominal trauma?

Dr. Allen's Diagnoses

Contusion of left kidney.
Fibroid tumor of uterus.
Fracture of spleen?

Anatomical Diagnoses

Ruptured spleen.
Uterine leiomyomas.

Pathological Discussion

Dr. Benjamin Castleman: Dr. Allen predicted exactly how the men on the service reacted. They did operate with the purpose of removing the pelvic tumor. As soon as they got down to the peritoneal cavity, before opening it, they could see large bluish masses through the peritoneal coat, so they realized that they would find blood in the abdominal cavity and forgot about the pelvic mass. On opening the abdominal cavity they found about 500 cc. of clotted blood, and in removing some of that they discovered that the source of the bleeding was the spleen, which had been covered with omentum and tamponaded, just as Dr. Allen prophesied. After the spleen and all the blood had been removed, exploration of the pelvis showed that the mass was composed of two large pedunculated fibroids, which it was decided not to remove at that time.

The spleen contained two jagged tears — one about 7 cm. in length, extending in for about 1 cm., and the other about 4 or 5 cm. in length, extending into a large cavity filled with blood. On cutting the spleen another large hemorrhagic extravasation was noted, without apparent connection with an external rupture.

Do you think, Dr. Allen, that during the fall the pressure of the fibroids might have helped injure the spleen? I suppose it would have been more likely if the fibroids had been calcified.

Dr. Allen: I had not thought of that. I had assumed that the tumor was not large enough to play a role. Possibly such was the case. It does not take much more of a blow than this woman had to fracture the spleen. If she landed just right, the fall could have done it without any help from the fibroids.

I was much intrigued by the statement in the history about the fluid in the costophrenic angle that the radiologist saw in the fluoroscopic examination; it apparently does not show on the films. If that was true, it is good evidence that there was hemorrhage from something in that region, and the usual source would be the spleen.

Dr. Schulz: The reason that we do not see evidence of fluid on the films is, I believe, that the patient was prone or supine when the films were taken and in the upright position when fluoroscoped.

The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Owned by the Massachusetts Medical Society and Published under the Jurisdiction of the Committee on Publications

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Material for early publication should be received not later than noon on Friday.

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Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

RECONDITIONING PROGRAM

The battle of Waterloo, history tells us, was won on the playing fields of Eton, so much did the courage and discipline of his young officers contribute to the morale of Wellington's army. In a different sense, some of the future victories of our present war may have been won already on the football field of Harvard, for it is his practical experience in the reconditioning of athletes that has placed Colonel Augustus Thorndike, of Boston, formerly surgeon to the Harvard football team and more recently commanding officer of the 105th General Hospital, as director of the Reconditioning Division, created last year by the Surgeon General.

A program for this reconditioning of disabled soldiers, according to an editorial in the April 1 issue of the *Journal of the American Medical Association*, was given impetus in a two-day conference recently held at the Schick General Hospital, Clinton, Iowa, at which time the results of such a program, carried out for several months past, were demonstrated by the commandant, Colonel Dean F. Winn, and his staff.

Training for men to be returned to military duty or to be restored as quickly as possible to useful civilian occupations includes "physical reconditioning, educational reconditioning and emotional reconditioning." Physical exercises of the convalescent wounded are begun at the earliest possible time, and are based on a graduated system of calisthenics, drills, games and military training. At the same time, carefully planned programs for educational and emotional reconditioning are carried out by other well-trained personnel. In a nation whose able young manhood has almost entirely gone into the armed services, that irreplaceable segment of the population must be husbanded and guarded as the very strength of the country.

In an earlier stage of our supreme military effort, when we first began to gather our armies together and the lists of the rejected grew, emphasis was placed first on rehabilitation of the unfit, and then on prehabilitation — the correction of defects before examination, in order to minimize the number of rejections. This conservation of our effective manpower must continue, but as our forces gain battle experience, the inevitable shift must take place in favor of the salvaging of those whom battle has disabled.

More than ever before, great numbers of the disabled will be returned to full duty, others with invaluable battle experience will be made available for limited service and the majority of the remainder, it can be confidently expected, will find their places in useful civilian occupations.

CUTANEOUS SULFONAMIDE HYPERSENSITIZATION

The indiscriminate employment of local applications of sulfonamide preparations on cutaneous manifestations is creating a menace of considerable

proportions. Not only have many cases of contact dermatitis with extensive exacerbations of the original process been produced by such applications, but serious generalized reactions have been provoked. These preparations are being used widely, both by physicians and by laymen, for eruptions without regard to whether or not they are of bacterial origin, and the number of cases with an unfavorable reaction is increasing.

Although the figures thus far presented indicate that evidences of hypersensitivity develop in only 5 per cent of those in whom such local applications have been employed,[1] in the aggregate a great amount of disability, sometimes protracted, is being produced by the complications of sulfonamide therapy. Reports presented in the literature[2-4] indicate that hypersensitization to these drugs may be general as well as cutaneous and may be occasioned in some cases by previous oral administration, and in others by the local application of sulfonamide preparations to the skin. After this sensitization is once produced, a recurrence of the cutaneous or of the general disturbance may be precipitated either by oral administration or by local application to the skin, and it is well recognized that this hypersensitivity may be permanent. Thus the local use of sulfonamide preparations introduces a definite hazard to the later administration of sulfonamide preparations internally, perhaps for pneumonia, peritonitis or other serious infection.

Although the original cutaneous disturbance may be exaggerated by the use of a sulfonamide, it is often not recognized that the drug is the causal factor in such a flare-up, with the result that it is continued and the convalescence considerably prolonged. Furthermore, some of these patients may become sensitized to other therapeutic agents, to occupational factors or perhaps to bacteria or bacterial products, as well as to the sulfonamides. Some cases are reported to be accentuated by exposure to actinic rays, and even after the skin has become normal, subsequent exposure to sun may reactivate the cutaneous disturbance. Activation may even occur following fractional doses of roentgen rays.

These cases of hypersensitization have become so numerous and the possible consequences so disturbing that the Section on Dermatology and Syphilology of the Medical Society of the State of New York at its last meeting passed resolutions "strongly disapproving the indiscriminate use of sulfonamide drugs in relatively harmless diseases of the skin which can be satisfactorily treated by equally efficient drugs" and "condemning the use of prepared dressings containing sulfonamide drugs which are sold promiscuously." Shortly after these resolutions, the *New York State Journal of Medicine* commented editorially on the matter,[5] emphasizing the necessity of preventing or reducing to a minimum such reactions of the sulfonamides.

Cole[6] has recently reviewed the subject; he advises that "sulfonamides should not be administered locally for more than five days because of the danger of sensitizing the individual and perhaps later precluding internal sulfonamide therapy where the situation may involve a far graver disease."

Still more recently, Tate and Klorfajn[7] cite the British experience with sulfonamide hypersensitization. These authors indicate that dermatitis is apt to appear within fourteen days after beginning the application of sulfonamide preparations, that the person so sensitized has a group sensitivity to the various sulfonamide drugs, that there is an apparent allergy to sunlight following such a dermatitis and that desensitization can be achieved. In one case in which desensitization was attempted, the extreme hypersensitivity is shown by the fact that "when the [oral] dose was increased to 1/250 grain daily the eruption began to break out afresh." In another previously reported case the oral administration of 1/8 grain was followed in six hours by an eruption similar to the earlier rash. They advise that topical sulfonamide therapy "should be reserved strictly for cases where withholding it might endanger life or lead to deformity." Editorial comment in the same issue of the *Lancet* supports earlier conclusions that these drugs should not be used for eczematous subjects, should not be applied to any condition for longer than a week, and should be much restricted in use.

Thus, growing experience with the local use of sulfonamide preparations demonstrates that these agents should be used as topical applications only

on the advice of a physician, who should prescribe them with great care and for a short period. Furthermore, the risks of indiscriminate use should be widely publicized.

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MASSACHUSETTS MEDICAL SOCIETY

DEATHS

BARRETT — James A. Barrett, M.D., of New Bedford, died April 28. He was in his fifty-ninth year.

Dr. Barrett received his degree from the Maryland Medical College, Baltimore, in 1910. He was a member of the Massachusetts Medical Society, the American Medical Association, the New Bedford Medical Society and the New England Roentgen Ray Society.

His widow, a son and a daughter survive.

BULFINCH — George G. Bulfinch, M.D., of Brookline, died March 14. He was in his ninety-sixth year.

Dr. Bulfinch received his degree from Harvard Medical School in 1874. He was a member of the Massachusetts Medical Society and the American Medical Association.

A son, three grandchildren and one great-grandchild survive.

COCHRAN — John J. Cochran, M.D., of Natick, died May 1. He was in his forty-eighth year.

Dr. Cochran received his degree from Harvard Medical School in 1923. He was a councilor for the Middlesex South District Medical Society and a member of the courtesy staffs at the Newton and Framingham hospitals. He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow, two sons and two brothers survive.

CURTIN — John J. Curtin, M.D., of Waltham, died March 10. He was in his sixty-first year.

Dr. Curtin received his degree from Harvard Medical School in 1908. He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow survives.

FAILLACE — Gaetano Faillace, M.D., of Brookline, died February 19. He was in his seventy-second year.

Dr. Faillace received his degree from the University of Naples Medical School, Italy, in 1903. In 1920 he was decorated by the Italian government for outstanding professional services among Italians in Boston and New England. He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow, two daughters and two sons survive.

GILLESPIE — Norman W. Gillespie, M.D., of Dorchester, died April 28. He was in his fifty-sixth year.

Dr. Gillespie received his degree from Harvard Medical School in 1915. He served at the Beverly Hospital, Boston City Hospital, Children's Hospital, Boston Lying-in Hospital and Walter Reed Hospital. He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow and two daughters survive.

JOHNSON — Herbert S. Johnson, M.D., of Stoneham, died April 29. He was in his eighty-ninth year.

Dr. Johnson received his degree from Harvard Medical School in 1883. From 1897 to 1918, he practiced medicine in Malden, during which period he was a school physician, and on the staff of the Malden Hospital. In 1918, he gave up private practice to join the staff of E. L. Patch Company, manufacturers of pharmaceutical supplies. He retired in 1932. He was a former member of the Massachusetts Medical Society.

A daughter and two sons survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

DISTRIBUTION STATIONS FOR ANTIPNEUMOCOCCUS AND ANTIMENINGOCOCCUS SERUMS

Because of continued reductions in the demand for antipneumococcus and antimeningococcus serums, and the necessity of eliminating nonessential processing and distribution services for the duration of the war, the number of distributing stations for the above products has been reduced. The following three classes of stations will be maintained hereafter:

1. Stations *regularly supplied* with antimeningococcus serum and with antipneumococcus serum of the types indicated:

City	Station	Serum
Boston	Bacteriological Lab., State House	Antipneumococcus serum (Types I-33) Antimeningococcus serum
Worcester	Worcester City Hospital Board of Health	Antipneumococcus serum (Types 1, 2, 4, 5, 7, 8, 9, 14 and 18) Antimeningococcus serum
Holyoke	Providence Hospital	Antipneumococcus serum (Types 1, 2, 4, 5, 7, 8, 9, 14 and 18) Antimeningococcus serum
Haverhill	Hale Hospital	Antipneumococcus serum (Types 1, 2, 5, 7 and 8) Antimeningococcus serum
New Bedford	St. Luke's Hospital	Antipneumococcus serum (Types 1, 2, 5, 7 and 8) Antimeningococcus serum
Pittsfield	House of Mercy Hospital Sampson Memorial Hospital	Antipneumococcus serum (Types 1, 2, 5, 7 and 8) Antimeningococcus serum

2. Stations supplied with *emergency stocks* of antimeningococcus serum and of antipneumococcus serum (Type 1), *when adequate amounts of these serums are available*:

City	Station
Ayer	Community Memorial Hospital
Brockton	Brockton Hospital
Gardner	Henry Heywood Memorial Hospital
Greenfield	Franklin County Hospital
Hyannis	Cape Cod Hospital
Nantucket	Nantucket Cottage Hospital

3. Stations supplied with antimeningococcus serum in certain communities not listed above, where the demand for antimeningococcus serum has been relatively frequent. The appropriate stations will be provided with this serum for *emergency stock* so long as sufficient serum is available and the demand continues in the community.

WAR ACTIVITIES

INDUSTRIAL HYGIENE

Industrial Eye-Hygiene Program

The Industrial Hygiene Division of the United States Public Health Service, in co-operation with the offices of the National Society for the Prevention of Blindness, — the Joint Committee on Industrial Ophthalmology and Otolaryngology, — has been developing and carrying out a program in eyesight protection in industry. Assistant Surgeon Joseph Lo Presti was detailed to the National Society for the Prevention of Blindness in New York City in July, 1943, for this purpose.

In the past, work in this field for the most part has been directed along eye protection and safety lines. The equally important aspect of this broad field, visual job analysis, has not received the study or emphasis that it warrants. By job analysis is meant the correlation of visual skills or abilities of employees, with job performances based on various criteria, such as speed of learning rate of work, accuracy of work, amount of spoilage, absenteeism and accident proneness or frequency. In addition, no serious attempts have been made in the past to establish minimum visual requirements for different types of occupation. For these reasons the scope of the industrial eye-hygiene program was made broad enough to encompass and emphasize these aspects — in fact, to include all important aspects of vision in industry.

Because of the acute shortage of ophthalmologists and allied professional groups engaged in eye care and eye service, other methods of visual examination had to be adopted to reach a sizable number of the industrial population. Three so-called "screening devices" were found to be already available, one of which is still in the experimental stage of its development. In order to evaluate the reliability of one of these devices, namely, the Ortho-Rater, a study was conducted at Stevens Institute, Hoboken, New Jersey. A group of 336 first-term students enrolled in the drafting course were tested by means of a simplified clinical procedure and by the Ortho-Rater. From five to six minutes per subject was taken for the examination. Data from this study are now in the last stages of analysis and it may be tentatively concluded that this screening device can be practically employed in industry to study visual skills. A visit was also made to the Visual Institute at Purdue University, Lafayette, Indiana, where the Ortho-Rater was developed. Methods of obtaining vision data and correlating them with job performance were studied with a view to adopting some of them in field work.

A comprehensive industrial visual survey is now being carried out in Connecticut, operating through the Bureau of Industrial Hygiene, Connecticut State Department of Health. The objectives of this project are: to obtain a cross section of industrial vision practices in a typical, concentrated industrial region engaged largely in war work; to compare various methods of examination, particularly screening tests, for vision; to derive recommendations for methods of appraising and improving existing visual conditions of employees and to select plants that may serve as a pattern to be followed throughout the country. Six plants have been thoroughly studied to date in the Hartford region, the work being conducted through the medical department of each plant. Whenever practical, employees were tested by various screen procedures, including the Ortho-Rater and the Vector-graph; and, on one occasion, with the Telebinocular, data on visual acuity (distance and near) muscle balance, vertical and lateral (distance and near) color vision, depth perception (stereopsis) were obtained. In addition, the Industrial Eyesight Protection Appraisal Form (Publication No. 402B — National Society for the Prevention of Blindness) was filled out for each plant covered, after consultation with the person responsible for the eye program in the plant. Items checked on this form include:

Employee Data: General medical supervision and special provisions made for eye services; safety items; first-aid facilities; other special eye services, such as screening, periodic recheck and examination for particular exposures; and provision for supplying eye appliances.

Plant Job Data: Illumination, eye hazards and provision for eye safety and protection.

This appraisal form will be sent to at least 30,000 industries by the War Production Board. In line with this survey, and anticipating that industry will seek ophthalmologists to assist in correcting conditions that may be found, the National Society for the Prevention of Blindness, with the co-operation of the chairman of the Joint Committee on Ophthalmology of the American Medical Association, is planning a seminar on industrial ophthalmology to be held in New York City at an early date. It is hoped that this will bring forcibly to the attention of the management of industries the need for an adequate eye conservation program. — Reprinted from *Industrial Hygiene News Letter* (March, 1944).

CORRESPONDENCE

MIDDLESEX UNIVERSITY SCHOOL OF MEDICINE

To the Editor: Dr. Stephen Rushmore in a letter published in the March 2, 1944, issue of the *Journal*, states that "the background of the discussion" with the Council on Medical Education and Hospitals of the American Medical Association regarding the status of Middlesex University School of Medicine is characterized in the following quotation: " 'The Council did not feel justified in offering any approval or even encouragement in connection with your efforts.' " Removed from the context of frequent discussions held by the Council with Dr. Rushmore, this sentence gives an entirely erroneous impression of the attitude of the Council.

The implication of this reference and the remainder of Dr. Rushmore's letter is that the Council is concerned with factors other than the quality of instruction in considering a school for inclusion on the list of approved medical schools, and that the Council desires to avoid additions to this list partly by refusing aid and encouragement to new schools.

Aid and encouragement have repeatedly been given to developing medical schools by the Council. Within the past year the medical school of the Southwestern Medical Foundation and the Bowman Gray School of Medicine have been approved as four-year schools. The University of Utah has expanded into a four-year medical school and partly through the help of the Council gives every promise of developing an excellent program. There has been extended correspondence with state authorities and conferences in Alabama with regard to their new four-year school. Correspondence and conferences are also being held with at least three other groups in which encouragement, advice and aid have been given by the Council.

It is notable that in each of these instances the school seems to have well-conceived plans and reasonably adequate financial and other resources and shows promise of meeting at least the minimum standards of medical education.

It is the Council's responsibility and privilege to give aid, advice and encouragement to such situations. It is clearly also the Council's responsibility not to encourage ill conceived or inadequately supported ventures into medical education. The Council has had to assume this responsibility on more than one occasion in the past and will continue to do so in the future when necessary.

Victor Johnson, M.D., *Secretary*
Council on Medical Education and Hospitals
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OLD NAVAL MEDICAL COMMISSIONS

To the Editor: The National Naval Medical Center, of Bethesda, Maryland, is endeavoring to collect for its archives a complete set of commissions issued to Naval medical officers and signed by past presidents of the United States.

There is a small nidus now at the Center, and it is hoped to be able to build this up to completion. Through the Navy Department Library and the National Archives a few more have been located. I am asking you to insert this letter in the *Journal* with the idea that various libraries or individuals may have in their possession such old commissions and would be willing to turn them over to the Center. If such are found and the owners are so generous, there could be no more fitting enshrinement of them than their use for this purpose.

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